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PROGNOSTIC STRATIFICATION OF PATIENTS WITH CYSTIC FIBROSIS BASED ON CLINICAL FEATURES OF INITIAL PRESENTATION

Jeffrey Neil Katz

1984

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PROGNOSTIC STRATIFICATION OF PATIENTS WITH CYSTIC FIBROSIS BASED ON CLINICAL FEATURES OF INITIAL PRESENTATION

by

Jeffrey Neil Katz

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ABSTRACT

PROGNOSTIC STRATIFICATION OF PATIENTS WITH CYSTIC FIBROSIS BASED ON CLINICAL FEATURES OF INITIAL PRESENTATION

Jeffrey Neil Katz

1984

Clinical studies of patients with cystic fibrosis have documented considerable variability both in the constellations of symptoms present at diagnosis and in subsequent survival rates. No study to date has examined associations between clinical features apparent at presentation and subsequent outcomes defined in terms of morbidity as well as mortality. In the present study we have 1) characterized clinical features manifest by 89 patients upon enrollment in the Yale Cystic Fibrosis Clinic; 2) assessed with a clinical scoring system the status of each patient at enrollment and follow-up intervals of five and ten years; and 3) correlated clinical features at presentation with subsequent clinical scores. Our data indicate that patients presenting with steatorrhea and no respiratory symptoms had favorable courses with just 2 of 22 patients deteriorating substantially by five years. Meconium ileus was associated with a less favorable prognosis and the worst outcomes occurred in patients presenting with respiratory disease, with 16 of 49 deteriorating after five years. The initial score and age at presentation had no bearing on subsequent outcomes. We conclude that clinical features apparent at diagnosis are valuable prognostic indicators of the extent of morbidity and mortality in patients with cystic fibrosis.

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INTRODUCTION

Cystic fibrosis (CF) is the most prevalent lethal genetic disease in America. Since the initial descriptions of CF in the late 1930's[1] an extensive literature has been published on its genetic, biochemical, pathologic, and clinical features. Clinical studies have documented that patients with CF initially present with a variety of distinct constellations of symptoms.[2] Studies have also established that the survival of patients with cystic fibrosis varies widely as well, with some patients dying in infancy and others living into their 30's.[3] Few investigators have sought associations between particular presentations and subsequent survival; no study has examined relationships between clinical features at the time of diagnosis and subsequent outcomes measured in terms of morbidity, not mortality. The present study examines records of patients enrolled in the Cystic Fibrosis Clinic at Yale-New Haven Hospital, with the goal of discerning associations between clinical features at presentation and subsequent patterns of morbidity as well as mortality. In this introductory section, selected aspects of cystic fibrosis will be discussed to provide necessary background information for this study. More complete introductory discussions of the disease can be found in pediatric texts.[4]

General Features: In the United States, cystic fibrosis affects approximately one in every 2,000 live births among Caucasians and one in 17,000 among Blacks[5]. Both sexes are affected equally.[6] Neither the abnormal genetic locus (or loci) nor the fundamental biochemical lesion have been identified. Protean pathologic changes have been described, most due to excessively tenacious mucus secretions which block gland ducts and

acini.[7] This process often results in the typical triad of chronic obstructive pulmonary disease (COPD), exocrine pancreatic insufficiency, and elevated concentrations of chloride in sweat[2]. Dozens of other clinical conditions frequently accompany cystic fibrosis, including nasal polyps, sinusitis, biliary cirrhosis, and aspermia.[2]

Diagnosis and Clinical Heterogeneity: The diagnosis of cystic fibrosis rests upon finding elevated sweat chloride (greater than 60 mEq/liter as determined by the pilocarpine iontophoresis method of Gibson et al.)[8] with evidence of one or more of the following: COPD, exocrine pancreatic insufficiency, or a positive family history.[2]. However, it has become increasingly clear that not all patients with CF present as prototypically wasted children with steatorrhea, chronic cough, and recurrent pneumonia. Several distinct clinical presentations have been recognized. These can be found in Table 1, as the classification of clinical presentations in cystic fibrosis adopted by the European Working Group for CF in 1976.[9] It should be noted that rare patients are diagnosed on the basis of symptoms which are neither gastrointestinal nor respiratory, such as heat prostration with hyponatremia and hypochloremia, pansinusitis and aspermia.[2]

The presentation of cystic fibrosis is heterogeneous with respect to age as well as symptoms. Data from the Cystic Fibrosis Foundation Patient Registry reveal that among the 901 new diagnoses reported to the Foundation in 1979, 57% of patients were diagnosed by one year of age, 33% between one and 10 years, 6.5% between 10 and 20, and 3.5% after 20 years of age.[3] Interestingly, comparison with analogous data from 1969 indicates substantial changes. Among patients diagnosed and reported in 1969, only 47% of patients were diagnosed by one year of age, 40.7% between one and

TABLE 1

Classification according to symptoms present at the time of diagnosis (adopted by the European Working Group for Cystic Fibrosis)

I. Patients who came to diagnosis because of a positive family history. These comprised patients diagnosed at birth and those diagnosed later in life because of an affected sibling.

II. Predominantly gastrointestinal symptoms such as steatorrhea, rectal prolapse, abdominal pain, failure to thrive, avitaminosis. No clinical evidence of lung disease.

III. Gastrointestinal and pulmonary symptoms.

IV. Patients with predominantly pulmonary symptoms, including chronic cough, bronchitis, pneumonia, radiologic evidence of lung involvement.

V. Meconium ileus at birth requiring surgical treatment.

10 years, 10.9% between 10 and 20 years, and 1.4% after 20 years of age.[3] Thus, over the nine year period increases were observed both in the proportion of patients diagnosed early in infancy and in the number diagnosed in adulthood.

Several hypotheses can be offered to explain these changes. It is possible, for example, that the biological behavior of the disease could have changed over nine years. A more plausible explanation, accepted by most investigators, is that physicians have developed a heightened suspicion of cystic fibrosis. This would likely result in earlier recognition and diagnosis of active disease in infancy and more frequent recognition of adult cases that might have been missed by clinicians in earlier secular periods. It is important to note that patients diagnosed in adulthood enjoy a relatively good prognosis. Some investigators have suggested that these patients have a distinct mild variant of the disease, although this claim cannot be evaluated definitively by biochemical markers of severity or comparisons of genetic loci.[6] One could also argue that increased suspicion of cystic fibrosis has shed light upon a wider spectrum of disease than previously appreciated.

Treatment: Curative therapy does not exist for cystic fibrosis. Treatment is aimed toward preventing or eradicating specific disease symptoms and complications. In particular, clinicians attempt to maintain adequate nutritional status and to prevent the progression of pulmonary disease.[10,2] Complications such as rectal prolapse, biliary cirrhosis, diabetes mellitus, cor pulmonale, and pneumothorax are managed as they would be for other patients.

Treatment of gastrointestinal disease is relatively straightforward and has changed little over the last three decades. The cornerstones of therapy include dietary management, pancreatic enzyme supplementation, and vitamin supplementation.[10,2] While enzyme preparations have been made more convenient, studies have not found newer enzyme preparations to be substantially more effective than their predecessors.[11]

The treatment of respiratory disease is considerably more complex and controversial. Principal techniques include physical measures, aerosol therapy, and anti-microbial therapy. Most physicians strongly advocate chest physiotherapy, specifically percussion, postural drainage, and cough.[2] However, there has been little objective documentation of efficacy for these procedures.[2] Aerosol therapy rests on the assumption that hydration of tracheobronchial secretions will improve their rate of clearance from the lung and that administration of drugs by aerosol improves delivery to the tracheobronchial mucosa.[2] Continuous mist tent therapy has been regarded with varying degrees of enthusiasm since its introduction in the 1940's.[12] Its efficacy remains debatable, as studies of pulmonary function after nightly mist therapy have yielded conflicting results.[12,13] Intermittent aerosol therapy -- intended to deliver antibiotics, bronchodilators, and mucolytics -- has been used widely for over three decades. Again, controlled studies examining the efficacy of this treatment simply do not exist.[2]

The last two paragraphs indicate that no major advances have occurred in the treatment of gastrointestinal disease or in chest physio- or aerosol therapy. In sharp contrast, antibiotic therapy has advanced dramatically over the last four decades. In cystic fibrosis, antibiotic therapy is

intended to control S. aureus, a frequent pathogen in infants and young children with CF, and P. aeruginosa, the highly virulent organism usually emerging as the predominant pathogen in bronchial secretions later in the course of disease.[11]

It is useful to distinguish four historical periods in the antimicrobial therapy of respiratory disease in cystic fibrosis.[14,10] The first might be termed "pre-antibiotic" and ended with the introduction of penicillin in the early 1940's. The second era, lasting until 1948, was characterized by reasonable staphylococcal coverage with sulfa drugs and penicillin, but deficient treatment of pseudomonas. Tetracyclines ushered in the third era, during which many agents were developed providing good coverage of staph and moderate activity against pseudomonas. Finally, the introduction of gentamycin and semisynthetic penicillins in 1968 allowed much more effective treatment of pseudomonas for the first time. Recognition of these distinct treatment eras is critical to the design and interpretation of clinical studies because the secular period of diagnosis and treatment might be expected to affect outcome. This concept will be re-emphasized later in this study.

Prognosis: Associations between distinct prognoses and such factors as sex, race, and presenting symptoms will be discussed in detail in the literature review. The present section will simply capsulize recent data on the range of prognoses in patients with cystic fibrosis and will highlight changes in these figures over the last decade.

Survival data from the Cystic Fibrosis Foundation reveal the following findings:[3] In 1978, 10% of patients under care were older than 20 years of age. Cross-sectional life table analysis of the 1978 data indicate that

the median age of survival was 21. Corresponding data from 1969 reveal that 10% of the patients under care were more than 16 years old and the median age of survival by cross-sectional life table analysis was 14.3. These results point toward two findings which have been corroborated by others as well.[15,16] First, the prognosis for patients with cystic fibrosis is quite variable, with some patients dying in infancy, others surviving into their 30's. Second, the median age of survival has improved substantially over the last decade.[16] Data do not exist to allow a determination of whether morbidity patterns over the past decade have paralleled those noted for mortality.

Investigators have posited several explanations for the improvement in survival of patients with cystic fibrosis. First, the advances in antimicrobial therapy described above could account for better outcomes.[2] Also, the increasing number of patients diagnosed in adult years could have a distinct milder variant of the disease associated with a longer median survival age. The diagnosis of children at increasingly younger ages has allowed earlier treatment; some have claimed that earlier treatment leads to better prognosis.[17,18] While each of these arguments can be defended on intuitive grounds, they must be regarded as speculative as data do not exist to adequately evaluate the contribution of each of these factors to improvements in prognosis.

Goals and Aims of the Study: It is clear from the preceding sections that patients with cystic fibrosis vary considerably in the particular symptoms manifest at the time of diagnosis. It is also apparent that the range of clinical outcomes varies widely among these patients as well. The overall goal of the present study is to determine whether particular

constellations of symptoms manifest at the time of diagnosis are associated with distinct clinical outcomes.

The recognition of prognostically distinct subgroups of patients has important implications for clinical research and clinical practice. From a research standpoint, demographic studies and clinical trials of therapeutic interventions could be much improved by stratification of patients at the time of diagnosis into groups with distinct prognoses. Specific treatments may prove effective only in certain subgroups of patients and ineffective in others. Such subtle but crucial distinctions cannot be made presently. For the clinician, the ability to predict the approximate course of disease based on presenting symptoms would provide several advantages. First, clinicians could more meaningfully counsel patients and families as to the expected course of disease. Also, clinicians could more appropriately gauge the aggressiveness of their treatment and particular choices of intervention.

In order to achieve the overall goal outlined above, the data collection and analysis in this study have been guided by five specific aims: (1) characterization of the basic demographic features of the patients followed at the Yale-New Haven Cystic Fibrosis Clinic; (2) characterization of the baseline clinical status of each patient at the time of enrollment into the clinic, including historical data, symptoms, and signs. It is important to realize that except for the rare patient diagnosed after seven years of age, patients with cystic fibrosis are too young at the time of presentation to perform pulmonary function tests. Hence, baseline clinical characteristics cannot include PFT's, which have become the parameters of choice for following the progress of older patients; (3) numerical assessment

of the clinical status of each patient at enrollment and at follow-up intervals; (4) correlation of particular clinical features present upon enrollment with subsequent numerical assessment of outcome at five and ten year follow-up; and (5) correlation of clinical features of presentation with changes in outcome scores over five and ten year intervals. The methods used to conduct this study are described in the following section.

METHODS

I. Clinical Setting

The Yale-New Haven Cystic Fibrosis Center was established decades ago. However, detailed files of clinic notes have only been maintained since 1966 and the present clinic director has worked in the clinic since 1970. Funding is received primarily (60%) from Yale University with additional support from state allocation and a Cystic Fibrosis Foundation Grant.[19] The clinic personnel include the director -- a professor of pediatrics at Yale University with clinical and basic science research interests in cystic fibrosis; an associate physician director; a clinic laboratory technician (for sweat tests and pulmonary function tests); a social worker from the Department of Pediatrics; and a clinic secretary. In addition, Yale-New Haven Hospital pediatric housestaff and Yale medical students have the opportunity to rotate through the clinic.

Clinic is held twice weekly in the pediatric specialty clinics area of the hospital. All patients are urged to schedule at least four visits per year. Sicker patients are scheduled more often. While most younger patients and their families are quite compliant, young adults attend clinic less frequently, often yearly. At each clinic visit, patients are typically first seen by a nurse who obtains and records vital signs and anthropometric measurements. In addition, sputum cultures, chest x-rays, and pulmonary function tests are obtained at regular intervals. Presently, chest films are taken yearly and pulmonary function tests (for patients over seven years of age) are performed twice a year. Throat cultures are taken at each visit. These guidelines vary considerably with the severity

of the patient's illness. After routine testing, the patients are seen first by medical students and/or residents and then by the attending physician. Except for rare occasions, the clinic director sees every patient. Pertinent historical and physical findings are recorded (usually by the resident or student) on a prepared form. Hence, there is uniformity in the scope and quality of data obtained at each visit.

For each visit the clinic director dictates a note which includes pertinent historical, physical, and laboratory findings and changes in therapy. The note is based both on the director's assessment and the information recorded by other observers. Notes, laboratory result sheets, and hospital discharge summaries for each patient are entered into longitudinal files located in the director's office.

II. Population Studied

Patients seen in the Yale Cystic Fibrosis Clinic live throughout Connecticut, mostly in the southern part of the state. The patients represent a wide range of socioeconomic backgrounds. Patients are referred to the clinic through a variety of mechanisms: Often, a local practitioner who strongly suspects the diagnosis of cystic fibrosis sends the patient to Yale for definitive sweat testing and longitudinal care. Many patients have had positive sweat tests in work-ups at outlying hospitals and are subsequently referred for follow-up in the Yale clinic. Other patients are referred to Yale specialists for work-up of problems not initially felt to be cystic fibrosis. The Yale clinician might then order a sweat test or do so after consulting with the cystic fibrosis clinic team. Other referrals from within the institution include patients sweat tested during in-patient

work-ups, and patients referred from the Primary Care Center and the Neonatal Intensive Care Unit with presumptive diagnoses of cystic fibrosis.

Three groups of patients with cystic fibrosis are not routinely referred to the Yale clinic. One is comprised of three patients who were either newly diagnosed or referred to the medical center in their adult years. These patients are followed by the Pulmonary Service of the Department of Medicine in Yale's Winchester Chest Clinic. Another group not seen in the cystic fibrosis clinic is comprised of patients managed by their local pediatricians. The number of these patients is difficult to determine, but is estimated at less than 3% of patients with the diagnosis of cystic fibrosis who live in areas served by the Yale clinic.[20] The third group includes patients who die before they are able to enroll. These patients all have meconium ileus at birth and die within a few days. They comprise 25% of patients with meconium ileus at Yale and 4-5% of all patients known to have cystic fibrosis.[21]

III. Eligibility Criteria

Patients who enrolled in the Yale-New Haven Cystic Fibrosis Clinic during the interval 1966 through 1978 were eligible for the study. This secular interval was chosen for several reasons. Exclusion of patients enrolled before 1966 assured that the course of each patient could be followed in the longitudinal record system which was established in 1966. In addition, the antipseudomonal antibiotics developed after 1968 were available to each patient. (Note that although eight patients were enrolled in 1966-1967, pseudomonas colonization usually does not occur until after age five.)[22] Exclusion of patients enrolled after 1978 assured that all patients were followed for at least five years or until their deaths.

Finally, patients who were followed in another clinic before enrollment in the Yale clinic were excluded from the study. This criteria assured that all data were obtained and recorded in the Yale clinic.

IV. Diagnostic Criteria

Criteria for the diagnosis of cystic fibrosis include sweat chloride levels greater than 60mg (by the pilocarpine iontophoresis method of Gibson et al.)[8] and at least one of the following: a) chronic obstructive pulmonary disease; b) exocrine pancreatic insufficiency; or c) positive family history. These diagnostic criteria have been employed at Yale throughout the time of this study and are widely accepted in the pediatric literature.[2]

V. Patients Who Left the Clinic

Eight patients who were eligible for the study left the Yale clinic subsequent to enrollment. In each case, the patients departed because their families moved out of the area. In all but one of these patients, adequate assessment of clinical status at appropriate follow-up intervals was obtained by contacting physicians at the clinic to which the patients were transferred.

VI. Zero Time

The term "zero time" refers to the reference point in patients clinical courses at which the baseline state is identified and classified, and from which subsequent follow-up periods begin. We considered three possible zero times in this study: The time of diagnosis of cystic fibrosis; the time at which therapy was initiated; and the time of enrollment into the Yale clinic. The quality of information submitted by referring physicians who made the diagnosis of cystic fibrosis was highly variable. Some physicians submitted detailed notes listing signs and symptoms. Others

wrote just a sentence or two. Similarly, there was considerable variation in therapies prescribed by referring physicians prior to enrollment. Hence, in order to standardize both the data base and the medical interventions for all patients in the cohort, the time of enrollment into the clinic was chosen as the zero time. This choice guarantees that all data used in the study was obtained by the small clinic team and that all therapy initiated during the intervals studied was prescribed by the clinic team. We were concerned initially that the interval between diagnosis and enrollment would be considerable; however, review of the data revealed this interval usually was less than three weeks and always less than three months.

VII. Sources of Data

Three sources of data were utilized: Notes maintained by the clinic director, chest x-rays, and hospital discharge summaries. The clinic notes provided the bulk of information on features of the initial presentation and on subsequent outcomes. The content of these longitudinal notes was discussed earlier in this chapter. Chest x-rays were obtained from the Department of Diagnostic Imaging at Yale. Over 95% of the films requested were available for review. (The few remaining films were scored by the clinic director on the basis of official readings transcribed by the Department of Diagnostic Imaging.) Hospital discharge summaries were routinely placed in patients' files after discharge.

VIII. Data Gathering

Data were assembled in two separate steps: (1) extraction of information from the files onto prepared extraction forms; and (2) coding of pertinent information for computer analysis. Copies of both the extraction form and the coding form have been included as Appendices A and B.

Extraction was performed in the Spring of 1983 on a form designed to record all information pertinent to the basic goals of the study. The extraction form consisted of five section: (1) demographic information including name, address, gender, date of birth and enrollment, and parents' occupations; (2) pre-existing conditions such as family history of cystic fibrosis and co-morbidity; (3) a clinical itinerary of the principal illness consisting of a chronology of signs and symptoms attributable to cystic fibrosis, hospitalizations before and after diagnosis, signal events raising the suspicion of the diagnosis, and a chronological record of birth weights and percentiles; (4) appearance of specific signs and symptoms including a lengthy check list of findings derived from textbook descriptions of the disease. We included a category for "other" findings not on the list; and (5) follow-up data including the data of death and loss to follow-up.

Several specific items on the coding form required precise defining criteria, as follows: In section one, "premature birth" was restricted to babies born more than four weeks before the expected date of confinement. In section two, "signal events" included data which, in the documented opinion of the physician who made the diagnosis, raised a strong suspicion of the diagnosis of cystic fibrosis. In section three, clubbing was recorded as "mild" if there was nailbed erythema without actual change in the angle between nail and nailbed. "Moderate" and "severe" referred to gradations in swelling with "severe" indicating obliteration of the angle. "Cor pulmonale" was a clinical diagnosis made on the basis of typical physical findings but usually without the confirmation of catheterization data. "Meconium plug syndrome" referred to abdominal pain which was accompanied by a mass consistent with fecal impaction in the cecum or terminal ileum.

"Steatorrhea" was defined by the patients' report of bulky, foul-smelling stools without measurement of fecal fat. "Vitamin deficiency" was similarly defined clinically without serum levels. "Hypoproteinemia" and "biliary cirrhosis" were defined by both characteristic laboratory values as well as physical findings. The intervals between birth and the onset of symptoms were gleaned from historical information offered by patients and families at the first clinic visit. The accuracy of this data clearly relies upon the patients' and families' ability to recall correctly the onset of symptoms. Recall of early symptoms can, of course, be biased by the knowledge of this ultimate diagnosis.

Once extracted, most data was then transferred to coding forms for computer analysis. Two types of extracted data were not coded: The first includes data which were not reported consistently or were reported in vague terms for a substantial number of patients. An example of such "poor quality" data is the date of the initial suspicion of the diagnosis. This information turned out to be available for less than half of the patients. A second category of data not coded was information ultimately felt not to be helpful in realizing the goals of the study. Examples would include the dates of appearance of particular symptoms for patients in whom the symptoms occurred after zero time. Though potentially interesting, this post-zero time data was not felt to be critical to a study of relationships between zero time features and subsequent outcomes. In addition, a few items of data which were not initially extracted onto the prepared form were ultimately gleaned and coded. These included patients' height and the percentile values of height-for-weight and height-for-age. Percentiles

were obtained from standard charts prepared by the National Center for Health Statistics.

IX. Assessment of Outcomes

A. Outcome Measure

Outcomes were assessed in terms of morbidity. While most previous work has examined survival only, it was felt that analysis of morbidity might detect clinical changes which are crucial to management decisions yet which could not be appreciated by assessment of mortality. The Shwachman scoring system was used to assess morbidity. Developed in 1958 by Harry Shwachman et al.[14] this system of clinical evaluation assigns point ratings for each of four clinical attributes: Level of general activity (e.g., school attendance, vigor of play, fatigue); physical examination (cough, rales, clubbing); nutrition (height vs. weight, stool appearance, muscle mass); and x-ray findings (atelctasis, emphyema, infiltrates). For each attribute, 0-25 points are awarded, with 25 being normal. The scores are summed to a composite figure from 0-100 which reflects overall clinical status. Occasionally criticized as under-emphasizing pulmonary aspects, the Shwachman system is generally regarded as a reasonably objective, consistent, and pragmatic means of assessing clinical status in cystic fibrosis. The system is summarized in Appendix C.

The present study employed a common modification of the Shwachman x-ray scoring system. The Shwachman system for chest radiographs does not carefully prescribe the designation of point values and has not proven to be reproducible among different observers.[23] Many investigators have preferred to use the Brasfield scoring system, which has more explicitly stated scoring criteria and is documented to be reproducible.[23] The

Brasfield system (a description of which is included as Appendix D) assigns a maximum of five points in five categories: Air trapping, linear densities, nodular cystic lesions, large lesions, and overall assessment. Conveniently, it is also based on a maximum score of 25 points and can simply be substituted into the Shwachman score.

B. Frequency of Assessment

The clinical status of all patients entered into the study was assessed by modified Shwachman scoring at the time of enrollment and again after five years of follow-up. In addition, the 55 patients enrolled before 1974 were included in an analysis of ten year follow-up as well. It was felt that these intervals would provide meaningful time frames for predicting prognoses.

C. Clinical Categories

Five categories of scores were established based on the advice of several pediatricians, including the clinic director: 90-100 (considered excellent); 80-89 (good); 70-79 (fair); 50-69 (poor); and less than 50 (terminal). The categories correspond both to distinct levels of severity of disease and to distinctive management strategies. Patients with "excellent" scores were barely distinguishable from individuals without cystic fibrosis and required only routine check-ups. Patients in the "good" category suffered minor impairments and demanded occasional therapeutic intervention for acute exacerbations. "Fair" patients also had only minor compromise, but required more careful observation, occasional hospitalization, and more frequent therapeutic intervention. Patients in the "poor" category suffered significant morbidity, required hospitalization as often as bi-annually, and were seen in clinic every few

weeks. "Terminal" patients frequently used home oxygen therapy, contacted the clinic regularly because of acute exacerbations, were admitted several times each year to the hospital, and were in imminent danger of dying.

D. Changes in Clinical Category

Several clinicians including the clinic director advised us that in addition to the *single state* measurements of clinical status provided by the Shwachman score and clinical category, it would also be valuable to assess clinically meaningful *transitions* in clinical states. In particular, it would be important to appreciate transitions which required changes in clinical management. We accounted for such transitions by describing patients' courses as "stable" if the patients either remained in the same clinical category or improved over the interval studied, and "deteriorating" if the patients slipped into a lower clinical category. Because the clinical categories are distinguished by unique management strategies, the changes in category by definition required changes in management. Thus, changes in category are of central concern to clinicians. Assessments of change in clinical category were determined by comparing five year to zero time clinical categories for all 89 patients, and ten year to zero time categories for the 55 patients followed for ten years.

E. Process of E aluating Outcomes

The clinic director assigned Shwachman scores based upon data contained in the clinic notes. The director was blind to the goals of the study. The clinic director also scored the chest x-rays. It was felt that the most accurate and consistent scoring could be obtained from a single observer who was both blind to the goals of the study and familiar with the patients involved.

F. Statistical Techniques

Univariate contingency tables were used to identify features of the initial presentation which corresponded with distinct outcomes. The relative importance and interactions of the characteristics identified in the univariate analysis were then assessed in a multivariate analysis. Analysis was performed using the SAS program at the Yale Computer Center.

LITERATURE REVIEW

I. Introduction

This section will review the few published studies of patients with cystic fibrosis which address the fundamental goal of the present study: The search for relationships between clearly defined clinical features present at the time of diagnosis and subsequent clinical outcomes. Features examined by the authors whose works are reviewed include demographic data such as gender, race, age, and the secular period of diagnosis; objective measures of the extent of disease, such as chest x-ray and fecal fat content; and clinical symptoms, expressed as the presence or absence of particular organ system involvement. The outcome parameters in most of the studies to be reviewed consist of survival data. Only a few authors have assessed morbidity as well as mortality.

This review is intended to aid in the design of the present study in two ways. First, it is important to evaluate previously documented relationships between presenting features and subsequent outcomes. These findings, if validly reached and corroborated, can be incorporated into model hypotheses. Second, it is useful to appreciate methodologic problems that have plagued previous studies. Once recognized, the pitfalls can more easily be avoided. In accordance with these two goals, the criticism shall be directed toward assessing the validity of findings which might guide the design of the present study and toward identifying methodologic problems that can then be minimized.

This literature review will include papers on each of the demographic and clinical features of presentation which investigators have related to

subsequent outcomes. For the few areas in which more than one paper has been written, just one will be discussed in detail and discrepant findings of other works (if such exist) will be mentioned. Tables I and II summarize principal design features and findings of the studies reviewed. Note that five and ten year outcomes have been inferred from the data whenever possible. This information will be useful in comparing results of the present study in which outcomes are assessed at five and ten year intervals.

II. Influence of Demographic Factors on Prognosis

A. Gender

Several investigators[3,24] have analyzed the role of gender in predicting prognosis. The results of each study are consistent with those of Stern et al.[25] whose work shall be reviewed critically. The Stern group reported in 1976 on 95 patients who had been followed at the Case Western Clinic since their diagnoses in 1957-1961. Seven patients initially included in the cohort were lost to follow-up and consequently excluded from the analysis. Follow-up ranged from 13-17 years. The authors did not specify precisely how many patients of each sex were entered into the trial, nor did they comment upon the symptoms present or the age of each gender group at the time of diagnosis. Twenty-eight patients died, 16 of them females. Life table analysis of survival was performed through 17 years of follow-up. The authors generated curves plotting percentage survival vs. the number of years after diagnosis. These curves reveal that at five and ten years, the percentage of females surviving was actually higher than of males: 95% vs. 88% at five years and 85% vs. 78% at ten. However, at 16 years of follow-up, the survival curves indicate a male survival of 78% with female survival just 60%. This result is consistent with the

TABLE 1

Studies Focusing on the Associations Between Demographic Variables and Subsequent Outcomes

Feature	Race	Gender	Secular period	Age at diag.	Sibling pairs
Author	Stern	Stern	Huang	diSantagnese	Orenstein
Institution	Case Western	Case Western	Temple	NIH	Case Western
Year publ.	1976	1976	1970	1979	1977
Description of Patients	17 blacks enrolled 1957-74 followed 2-17 yr mean age at diag = 31mo 93 white controls enrolled 1957-61 followed 15-17yr	95 patients #males not given enrolled '57-61 followed 13-17yr 1 lost to follow up Ages not given	37 patients 24 male 22 dx by age 1yr enroll 1952-57 73 patients 37 male 28 dx by age 1yr enroll 1957-62	75 patients 41 male ages, yr of enrollment, duration of follow-up not given	16 pairs enrolled 1957-77 followed to age 7 older sibs over 1 yr at diagnosis younger sibs less than 1 yr at diagnosis
Results	*5yr survival for blacks and whites around 95% *10 yr survival: blacks 95% whites 80%	*5yr survival: male 88% female 95% *10yr survival: male 78% female 85% *16yr survival: male 75% female 60%	129 patients 48 male 50 dx by 1yr enroll 1962-67 5 yr survival: '52-57:35% ±8 '57-62:64% ±6 '62-67:77% ±7	Correllation of age at dx with Shwachman score: -0.01 P = .49	At 7 years of age younger sibs have better PFT's and CXR
Conclusions	CF milder in blacks		difference in secular intervals	age at dx not related to clinical score	Early diagnosis leads to better prognosis
Comment (See text)	small group brief follow-up secular interval	Females deter. in teens age at diag. presenting symptoms	short follow-up stratified analysis	Residue cohort	Age at diagnosis genetic homogeneity

* Survival inferred visually from graph presented in paper. Data are estimates and error is not known.

observation, made by several others[3,24] that survival among females deteriorates in the teenage years. The results would be much stronger if the authors had considered the age of diagnosis and the presenting symptoms in each gender group. Also, the survival curves have diminished statistical reliability at 16 years of follow-up because some patients were followed for less than 16 years. We are not informed of the number of patients followed 16 years, but are told that the minimum follow-up was 13 years and maximum 17 years.

B. Race

Race is seldom considered in studies of cystic fibrosis as 97.2% of diagnosed and reported patients in the U.S. are white[3]. In 1976, Stern et al.[5] of Case Western compared 17 black patients diagnosed between 1957 and 1974 with 93 white controls diagnosed between 1957 and 1961. The mean age at diagnosis was two years seven months for the black patients and was not given for the whites. Presenting symptoms were not mentioned. Forty-five percent of the blacks were male while the sex ratio in controls was not given. Follow-up duration differed markedly in the two groups: 2-17 years among the blacks; 15-17 years among the controls. Only one of the blacks and 28 of the controls died. Life table analysis generated survival curves which indicated that five year survival for both whites and blacks was around 95%. However, at ten years of follow-up, the survival of whites was 80% while that of blacks remained around 95%. The authors concluded that the course of cystic fibrosis in blacks is milder than in whites.

These conclusions simply cannot be accepted because of methodological problems. First, the secular period of entry into the study differs markedly. Blacks were entered as late as the mid 1970's while all whites

were diagnosed and entered in the late 1950's. As was described in the introductory chapter, antibiotic treatment and diagnostic acumen likely improved over three years; hence, one cannot exclude the possibility that differences in treatment and diagnosis of milder variants accounted for the results in this study, rather than race. The second problem, also severe, concerns the use of life table analysis in a group of only 17 patients, with only one death, followed for as short a time as two years in some cases. With numerator and denominators so small, the potential for misleading estimates is quite large.

C. Secular Period of Diagnosis

The issue of the secular period of diagnosis, central to the preceding study, was examined directly by Huang et al. of Temple in 1970.[26] The authors identified three distinct secular periods in the treatment of patients with cystic fibrosis at St. Christopher's Hospital for Children. Prior to 1957 patients were treated with pancreatic enzymes and intermittent antibiotics, but without sustained intensive follow-up. In 1957, a cystic fibrosis clinic was established at St. Christopher's to provide close follow-up and long-term antibiotic therapy. In addition, the use of aerosol medication was introduced around 1957. In 1962, the clinic funding was bolstered and a more intensive program was developed including mist tent therapy, physical therapy, and improved dietary management. The Huang group hypothesized that treatment improved over these successive intervals, resulting in enhanced long-term survival.

The authors sought to test this hypothesis. They examined mortality data of three cohorts of patients: (I) 37 patients admitted for treatment between 1952 and 1957. Twenty-four of the 37 were male and 60% were diagnosed

before age one; (II) 73 patients admitted to the St. Christopher's clinic between 1957 and 1962. Thirty-seven (49%) of these were male and 38% were diagnosed before age one; (III) 129 patients diagnosed between 1962-1967. Forty-eight of these were male (39%) and 39% were diagnosed before age one. Of note, the authors do not specify the interval between diagnosis and admission for treatment. They also provide no information on the number of patients lost to follow-up. They do divide the patients into two clearly defined groups based on the severity of pulmonary involvement at first observation ("mild to moderate" and "severe"). This determination is based on history, physical exam, and x-ray. The authors do not provide the precise criteria used for the division.

Life table analysis revealed that after five years of follow-up survival in group (I) was 35% (± 8.9); group (II) survival was 63.6% (± 6.4); and in group (III) 70.6% (± 7.0). Groups (II) and (III) were analyzed further by stratifying according to age at diagnosis, sex, and severity of pulmonary disease. No explanation is given for the exclusion of group (I) from these analyses, although it seems likely that there were insufficient patients in the cohort for meaningful subdivision. Patients with "mild to moderate" lung disease at presentation had much better five year survivals than patients with "severe" lung involvement, 88.4% vs. 35.0% in group (II); 92.6% vs. 21.2% in group (III). The clinical criteria for these categories are not given. The difference in survival between children first observed at less than one year was not statistically different from those admitted to the clinic after one year of age (61.5% vs. 67.5% in group (II); 79.8% vs. 73.8% in group (III)). Analysis of sex distribution revealed that in group (II) five year survival of females was better than males (74% vs.

44%) while in group (III) the males had better survival (82.4% vs. 69.5%) though the difference was not statistically significant ($P > .05$). Huang et al. interpret their data to indicate primarily that patients treated in the later secular intervals had better outcomes. They also conclude that extensive pulmonary disease at presentation is a poor prognostic indicator.

The primary conclusion -- that patients who enrolled in later years fared better -- is difficult to evaluate because group (I) was not stratified according to sex and age at diagnosis. This is particularly important because the sex ratio and ages of patients in group (I) are so markedly different from those in the other patient groups. The poor five year survival of males in group (II) (44%) raises the question of whether outcomes in the predominantly male group (I) can be explained on the basis of sex, not secular period. The study would also be more meaningful if the chronological relation between diagnosis and entry into the study were clarified. Furthermore, survival data, while important, do not detect crucial changes in clinical status. Clinicians make management decisions based on morbid events. Hence, assessment of outcomes in terms of morbidity would be more valuable for clinicians than mortality data alone. As a result of these criticisms, conclusions must be tentative: The study indicates that the secular period of entry into the clinic must be scrutinized for its potential effect upon five year survival.

D. Age of Diagnosis

While the Huang group's cursory analysis of the age at diagnosis provided no definitive information it suggested that the age at diagnosis had no predictive prognostic value. diSantagnese et al.[27] (1979) of the National Institutes of Health (NIH) attempted a more complete evaluation

of this relationship. The group studied 75 patients over 18 years of age followed at the NIH clinic. Fifty-five percent of the group was male and 21% were diagnosed after age 15. Presenting symptoms were not mentioned. Of crucial importance, the patients studied comprise a residue cohort admitted to the clinic at age 18 rather than an inception cohort followed since diagnosis. Correlation of age at diagnosis with Shwachman scores in 1979 (after a variable period of follow-up) revealed a correlation coefficient of -0.01 at a P value of 0.49. The authors conclude that the age of diagnosis is not correlated with clinical score. For the present study, these results and conclusions have negligible value. The relationship between information available at presentation and subsequent outcome cannot be studied in a residue cohort because many patients could have died or been lost to follow-up and were overlooked in the analysis. Hence, a reliable study of the relationship between the age at presentation and subsequent outcome remains to be completed.

E. Comparison with Siblings

In a study purported to demonstrate the effect of early diagnosis and treatment on clinical outcomes in cystic fibrosis, Orenstein et al.[18] (1977) studied 16 sibling pairs in their Case Western clinic. The 32 patients were diagnosed between 1957 and 1970. To qualify for the study, the older siblings must have been diagnosed after age one and the younger siblings before age one. Fifteen of the 16 older siblings and nine of the younger siblings had pulmonary disease at diagnosis. Fifty percent of the older siblings were male as were 44% of the younger siblings. No patients died and each was followed until age seven, the endpoint of the study.

Comparison between siblings was made using various outcome measures at age seven. These included chest x-rays, Shwachman scores, pulmonary function tests (PFT's), and anthropometric measures. Data were analyzed using the paired student's t-test, with ordered pairs being (older sibling - mean/mean of the two siblings, younger sibling - mean/mean). The authors concluded that the younger siblings had better total scores than the older siblings ($P < 0.05$). Twelve of the younger siblings had higher scores at age seven. Average score for the 16 older siblings was 70 and for the younger siblings was 86. The younger siblings also had lower residual volumes and RV/TLC ratios ($P < 0.05$). In these categories, the younger sibling's score was better in 12 and 11 of the 16 pairs, respectively. Eleven of the younger siblings also had higher chest x-ray scores (Shwachman scores). Seven of the older siblings had chest x-rays of 16 or below compared with none of the younger siblings. The authors concluded that the younger siblings fared better and inferred that early diagnosis and treatment leads to better clinical outcomes.

While these results indicate that younger siblings had better clinical outcomes in this study, inferences about the effect of early diagnosis and treatment simply cannot be made for several reasons. First, pairs in which the older sibling was diagnosed before age one were excluded from the study. This exclusion eliminates patients whose natural histories might have differed markedly from the older siblings studied. Of course, if the natural course of disease were identical between siblings, as the authors assume, this exclusion would not bias the results. But there is simply no evidence to suggest that in siblings the natural course of cystic fibrosis is identical or even similar.[28] The authors failed to bolster their assumption

of homogeneity among siblings with comparisons of symptoms at presentation and later in the course. To conclude, the effect of early diagnosis on prognosis simply cannot be addressed by a study of sibling pairs.

III. The Relationship Between Clinical Data Obtained at Diagnosis and Subsequent Outcomes

A. Normal Pancreatic Function

Only a few investigators have studied the relationships between either physiologic measure of disease or symptom status at diagnosis and subsequent clinical outcomes. Gaskin et al.[24] (1979) retrospectively examined 72 patients diagnosed between 1962 and 1980 having normal pancreatic function as determined by fecal fat excretion. This group was compared with an unspecified number of patients with steatorrhea who were enrolled in the clinic at the time of the study. The 72 patients with normal fecal fat excretion consisted of 42 males and had a mean age at diagnosis of five years. All patients in the study were at least seven years old at the time of analysis -- the age at which pulmonary function studies are first performed. The sex ratio of the controls was not given nor was the age at diagnosis nor mode of presentation. Interestingly, some of the patients with normal fecal fat excretion presented with loose stools.

The authors compared PFT's (FEV_1, FEV_{25-75}, RV/TLC) arterial blood gases and the percentage of ideal weight for height among patients in four groups defined by presence or absence of steatorrhea and by sex. Data were obtained at six month intervals after age seven and plotted against patients' ages. Least squares regression lines were generated for the four groups for each of the clinical variables studied. Differences in slopes were then analyzed. In this manner the authors demonstrated that patients with

TABLE 2

Studies Focusing on the Associations Between Clinical Variables and Subsequent Outcomes

Feature	Fecal fat excretion	Highest 1st yr x-ray score	Organ system involvement
Author	Gaskin	Stern	Kraemer
Institution	Toronto	Case Western	Berne, Switzerland
Year published	1982	1976	1977
Description of Patients	72 cases with normal fecal fat enrolled 1962-73 42 males mean age at diag = 5yr no description of controls with high fecal fat	95 patients enrolled 1957-61 followed 14-18 yrs 7 lost to follow-up Two groups: I. initial xray ≥ 19 II. initial xray < 19	204 patients enrolled 1956-76 followed 1-20 years age at diagnosis and results are displayed in text
Results	Patients with normal fecal fat have better PFT's Females do worse after ten years	*5 yr survival: I: 98% II: 82% *10 yr survival: I: 94% II: 60%	
Conclusions	as above	low initial xray score leads to poor outcomes	respiratory involvement at enrollment bodes poor prognosis
Comment (See text)	Residue cohort age at diagnosis secular period statistics suspect	age at diagnosis role of gender survival data	mortality only family history group heterogeneous

*Estimated from graph of data. Error not known.

normal pancreatic function did better than controls in each of the categories studied. Among patients with steatorrhea, girls did worse than boys, the differences becoming apparent at around 15 years. For example, the regression for FEV_1 revealed that at ten years males and females with normal pancreatic function had values of around 95% of normal while males and females with steatorrhea had values around 85% of normal. However, the regression lines at 25 years of age showed males and females with normal pancreatic function hovering around 90% while males with steatorrhea had FEV_1 of 60% and females 40% of normal.

The study, while fascinating, is quite problematic. First, cases have been entered over the secular period 1962-1980, which spans different eras in the treatment of cystic fibrosis. This tactic was criticized earlier in this review. Also, it would be extremely important to learn the average age at diagnosis of the patients with steatorrhea. Given the relatively late age of diagnosis of patients with normal fat excretion (five years), one wonders whether age of presentation might be an even stronger predictor of pulmonary function than pancreatic function. In addition, neither group is an inception cohort of patients diagnosed and then followed; rather they are residue cohorts of patients available for PFT's after age seven. Hence, information is lacking as to how many patients died before age seven or were lost to follow-up.

Finally, the statistical methods are questionable. The regression lines are displayed extending from ages seven to thirty. However, it is not clear how many, if any, patients lived to age 30. The authors do not even compare the present ages or average lengths of follow-up in each group. Most important, they present no evidence that changes in pulmonary function

studies vary linearly with age in cystic fibrosis. The assumption of linearity is central both to the impressive graphic results and to the numerical calculations. To summarize, the authors present an interesting subgroup of patients clearly defined at diagnosis by laboratory measurement of fecal fat. They claim that this group enjoys better subsequent pulmonary function than age-matched controls, but unproved assumptions underlie their arguments.

B. Chest X-Ray Scores

The prognostic value of initial chest x-ray scores was evaluated by Stern et al.[25] (1976) in a study of 102 patients admitted to the Case Western Clinic between 1957 and 1961. Seven patients were lost to follow-up and were not included in the analysis. Twenty-eight died and 67 continued to be followed at the time of publication. The patients were divided into two groups based on their highest chest x-ray scores over the first year of follow-up. This strategy was designed to distinguish between acute reversible findings at presentation and chronic lesions that persisted for a year. The authors fail to indicate the frequency with which chest x-rays were obtained during the first year of follow-up. Group (I) consisted of patients with at least one chest x-ray score greater than or equal to 19 during the first year. (The Shwachman scoring system was used, with a maximum score of 25 points.) Patients in group (II) had first year scores consistently below 19. The sex distribution in the group is not given nor is the nature of clinical presentation. Age at diagnosis among patients in group (I) averaged 20 months for males and 38 months for females. In group (II), males were diagnosed at an average age of 102 months and females at 60 months of age.

Survival curves were calculated using life table analysis. Interpretation of the curves reveals that five year survival was around 98% for group (I) and 60% for group (II). Ten year survival in group (I) was around 95% and in group (II) 60%. The authors concluded that the presence of irreversible pulmonary disease predicts poor long-term prognosis.

While the data strongly suggest that persistent x-ray abnormalities bode a poor prognosis, the analysis is not thorough enough to implicate irreversible pulmonary disease as the culpable factor. The patients should have been stratified by sex, a variable known to influence prognosis. In addition, the widely discrepant ages at diagnosis of patients in the two groups raise the question of whether age is the factor with most predictive power. The chest x-ray score could simply serve as a surrogate reflection of patients' ages at diagnosis rather than as an independent measure of the severity of pulmonary disease. Again, further analysis would be required to resolve this issue. Finally, as has been mentioned already in this review, survival data provide an incomplete assessment of clinical outcomes.

C. Organ System Involvement

Only one study to date compares outcomes in patients stratified by organ system involvement at the time of diagnosis. Kraemer et al.[9] (1977) studied 204 patientsretrospectively who enrolled in the Berne Clinic between 1956 and 1976. They did not specify the sex of patients nor the average duration of follow-up. The patients were divided into five groups based on symptoms present at the time of diagnosis. The groups consisted of: (I) Patients diagnosed because of a positive family history. Some of these were diagnosed in the first months of life because they were born into families with members known to have cystic fibrosis. Others were diagnosed

at a later age after the diagnosis of an affected sibling; (II) Patients with gastrointestinal symptoms without clinical or radiological evidence of lung disease; (III) Patients with both gastrointestinal and pulmonary disease; (IV) Patients with predominantly pulmonary symptoms; and (V) Patients with meconium ileus at birth necessitating surgery. The mean age of diagnosis was 3.3 months for patients in group (I), 16.3 months for group (II), 27.5 months for group (III), 21.1 for group (IV), and just days for patients with meconium ileus (V).

The authors constructed curves of cumulative survival rates calculated from the day of diagnosis. They did not, however, indicate the number of deaths among the 204 patients. These curves depict five and ten year survival rates as follows:

Group	Presentation	N (%)	Age At Dx	5 yr. Survival	10 yr. Survival
I	positive family history	15 (7)	3.3 months	88%	70%
II	meconium ileus	37 (18)	days	15%	10%
III	gastrointestinal symptoms	32 (16)	16.3 months	83%	60%
IV	g.i. and resp. symptoms	58 (29)	27.5 months	72%	55%
V	respiratory symptoms	62 (31)	21.1 months	48%	32%
		204 (100)			

The authors concluded that patients presenting solely with pulmonary symptoms have a particularly poor survival. They explained the very poor survival in children with surgically treated meconium ileus by implicating perinatal and post-operative mortality. Indeed, their data reveal that 90%

of the ten year mortality in this group occurred in patients less than one year of age.

The results are limited by several methodological problems. The authors combined patients diagnosed at widely disparate secular periods. Also, they restricted outcomes to mortality without considering morbidity. They failed to stratify patients by sex or by the severity of disease at presentation. In addition, the statistical validity of the life table data cannot be evaluated critically without knowledge of the number of deaths.

Finally, the group who came to diagnosis because of a positive family history (I) poses problems in the interpretation of results. The authors mention that some of these patients were entirely asymptomatic when diagnosed in the first months of age on the basis of a genetic risk known at birth. Others were diagnosed later on, after the recognition of an affected sibling. The latter group may well have had signs and symptoms attributable to cystic fibrosis upon diagnosis, though these disease manifestations were not recognized as such. Hence, the group is not homogeneous with respect to clinical status at diagnosis. Some may have had symptoms, other may not have. It would be more useful in a study of the prognostic value of clinical symptoms at presentation to classify as "asymptomatic" only those truly without symptoms and to categorize others, regardless of the impetus for diagnosis, according to the symptoms present at the time of diagnosis. Hence, the symptom classification of the European Working Group for Cystic Fibrosis,[9] upon which the Kraemer study was based, is inappropriate for studies relating initial clinical features to prognosis.

One particular finding merits especially close attention. The data suggest that patients with both gastrointestinal and pulmonary disease at

presentation fared better than those with pulmonary disease alone. Several interpretations come to mind. Differences in the secular period of diagnosis and the gender composition of the two groups, not examined by the authors, could have had an effect on clinical outcomes. One might also suspect that the better outcomes in patients with gastrointestinal as well as pulmonary symptoms was due to earlier diagnosis. However, the group with gastrointestinal and pulmonary symptoms was in fact diagnosed at a later mean age. The two groups could also differ in the severity of pulmonary disease at presentation, or the rate of progression of disease or both. The data are also consistent with the notion that the two groups represent distinct variants of the disease with unique presentations and outcomes. These hypotheses are not mutually exclusive. Suffice it to say that the "beneficial effect" of gastrointestinal symptoms on patients also having pulmonary symptoms requires more rigorous analysis.

IV. Summary and Conclusions

This review has examined critically the existing literature on relationships between clinical features present at diagnosis and subsequent outcomes. The findings of these studies have been evaluated and methodologic problems noted. The results of this literature review have guided the design of the present study, as shall be discussed in this concluding section.

A. Evaluation of Previous Work

While each of the studies reviewed had defects which limited the validity and/or interpretations of results, several conclusions can still be reached based upon the data presented. With respect to gender, the Stern group[25] documented a result which has been consistently reported by many

investigators -- that gender seems not to play a role in survival until the teenage years when the females do markedly worse than males. While the study is flawed, it is fair to conclude that the effect of gender should be evaluated in the present study as potentially affecting outcome, especially in teenage years. The Stern group[5] also raise the question of whether the natural course of cystic fibrosis is milder in blacks. Their study does little to clarify the issue. The present study will not be helpful either, as only two of the patients entered into the study are black.

The work of Huang et al.[26] indicates that the secular period of diagnosis may have an independent effect on prognosis. The authors' conclusions cannot be accepted until other variables such as gender and age at diagnosis are shown to be responsible for the impressive mortality in the group diagnosed during the earliest time interval. However, while inconclusive, the results warn that the secular period of diagnosis should be considered as potentially influencing subsequent outcomes. The patients' ages at diagnosis, a variable which would seem on intuitive grounds to have an effect on post-diagnosis outcomes, has yet to be tested adequately. Certainly, the study by diSantagnese[27] of a residue cohort does not resolve the question. This variable will be examined carefully in the present study.

Among studies of more clinical features of the presentation, the interesting study of Gaskin et al.[24] has the least practical value for the present work. The authors' analysis of patients classified according to fecal fat measurement has little value in the absence of this laboratory parameter (which is not available for patients enrolled at Yale). In fact, the presence of patients with loose stools in the group with normal fecal fat excretion indicates that the Gaskin results cannot be extended to groups

of patients defined by gastrointestinal symptoms in the absence of laboratory testing.

The work of Stern et al.[25] on patients subgrouped according to x-ray score is much more valuable for the present study. This paper indicated that significant radiological lesions which persist through the first year portend poor survival rates. The issue left unresolved by these authors is whether their results can be ascribed to a fundamental difference in severity of disease among patients. The other possibility, suggested by the advanced age of the group with worse x-rays, is that these patients were simply diagnosed later in the course of the disease. Regardless of the explanation, the finding indicates that patients with advanced pulmonary disease at diagnosis have lower survival at discreet intervals after diagnosis.

Finally, the paper of Kraemer et al.[9] most clearly approximates the intent of the present work. These authors also documented that the presence of pulmonary symptoms at presentation was associated with worse survival. The study also points to gastrointestinal disease as conferring a "beneficial" effect on the survival of patients presenting with pulmonary disease. The reproducibility and explanation of this interesting result remain to be established. The present study shall examine this finding. The Kraemer study examines only mortality with no consideration of morbidity. Hence, no study to date has analyzed associations between presenting symptom clusters and subsequent morbidity. The present study shall attempt to fill that gap.

B. Methodological Defects to be Minimized

Several methodological problems were identified in this review with the intent of avoiding them in the present study. First, the variables known or suspected to have an effect on prognosis must be controlled for. These potentially predictive factors include gender, secular period of diagnosis, age at diagnosis, severity of pulmonary disease, and other organ system involvement. In addition, the group of patients studied must be an inception cohort followed since diagnosis rather than a residue cohort assembled at a later point in time. The criteria for categorizing patients must be sensible and explicitly stated. For example, the group in Kraemer's study defined as having a positive family history does not necessarily share the same clinical manifestations (or lack of them) at diagnosis and hence would be inappropriate for the present study.

Finally, outcome events should be clinically relevant and studied at suitable intervals. Restricting the study to survival eliminates consideration of morbidity status which is critically important to patients, physicians, and families. The present study will consider a wider range of clinical outcomes by analyzing morbidity as well as mortality.

RESULTS

I. Introduction

This chapter presents the major results of the study. Raw data are arranged in tables located at the end of the chapter. The results shall be explained in the following sections with emphasis on those findings which are either particularly germane to the central issues of the study or discrepant with previously reported data.

Two distinct cohorts of patients have been studied. The first includes 89 patients who enrolled between 1966 and 1978 and have thus been followed at least five years but less than ten years. This cohort shall be referred to as the "five year" group. The second cohort, the "ten year" group, is comprised of 55 patients enrolled between 1966 and 1973. These patients were followed for at least ten years. Although the ten year cohort is a subset of the five year group, it is important to recognize that differences could potentially exist in the compositions of the two groups and in their clinical outcomes. Hence, results obtained from study of the five year cohort do not necessarily apply to the ten year group and vice versa. For these reasons, the two groups will be discussed and analyzed separately.

II. Results of the Five Year Cohort

A. Description of the Cohort

1. Demographic features: Table I presents demographic features of the five year cohort, including gender, race, the number of affected siblings, age at zero time, and the secular period of diagnosis. Half the patients were female and almost all (98%) were white. The mean age at zero time was 32 months (± standard deviation of 49) and the median age was 13

months (range 1-250). The discrepancy between mean and median values suggests that as in other series[9] the age at zero time of patients in this cohort generally clustered between one month and two years, with the tail of the distribution stretching out to 20 years. Note in Table I that patients were enrolled at a rather constant number from 1966-1978, six to eight patients per year.

2. Select clinical features at zero time: We determined the prevalence at zero time of several clinical features which we suspected to be associated with distinct clinical outcomes. This suspicion was prompted both by the advice of clinicians and by reported studies.[22] The features included co-morbidity, clubbing, and throat culture results. Results are presented in Table II. Of the 89 patients, only six had one of the listed co-morbid diseases; 14 had moderate to severe clubbing; and 11 grew out pseudomonas aeruginosa. The throat culture results must be interpreted with caution, as throat specimens do not ideally reflect sputum flora.[29]

3. Symptoms at zero time: Since the analysis is based largely on the particular symptoms present at enrollment, we examined the distribution of respiratory and gastrointestinal symptoms in the cohort. The results are presented in Table III. We suspected that a division of the patients with respiratory symptoms into two groups defined by the anatomic site of pathology might reveal prognostic distinctions. Hence, respiratory symptoms are subgrouped into "alveolar" and "upper airway" categories. Patients presenting with acute pneumonitis or with at least two prior episodes of pneumonia were categorized as "alveolar". Patients without alveolar disease were categorized as "upper airway", and typically presented with histories of cough, wheezing, or at least two episodes of

bronchitis. Patients with alveolar disease could have had symptoms referable to the upper airway as well.

Patients with gastrointestinal disease were also subgrouped. It has been recognized that patients with meconium ileus generally have worse outcomes than patients with steatorrhea.[9] Among 14 patients with meconium ileus, those with peritonitis or requiring resection have been reported to do worse than patients without these complications.[4] Hence, we noted the frequency of patients who fell into three groups: Meconium ileus with resection or peritonitis (5); meconium ileus without these complications (9); and gastrointestinal disease other than meconium ileus (65). The latter group shall be referred to simply as "steatorrhea" since this symptom is present in all the patients in the group. All but ten of the 89 patients had gastrointestinal symptoms at referral to the clinic, most without meconium ileus. Recall that meconium ileus may be under-represented in our study, as patients with meconium ileus who die at birth are not enrolled in the clinic and therefore are not included.

4. Clusters of symptoms at zero time: A major goal of the study was to analyze constellations of zero time findings, not just isolated symptoms. Therefore, patients were stratified into five groups defined by the clusters of symptoms present at zero time. The distribution of patients into these five groups is presented in Table IV. Only two patients were diagnosed on the basis of a positive family history and found to have no symptoms at zero time. These patients were grouped under "family history, asymptomatic". Four other patients were diagnosed on the basis of a positive family history but were noted to have other symptoms as well. These patients were grouped according to the symptoms present at the time of enrollment.

As noted in the literature, patients diagnoed on the basis of a positive family history have been lumped together in other series.[9] A quarter of the patients had isolated steatorrhea with no respiratory disease at presentation. Eight of 89 had isolated respiratory disease with no gastrointestinal involvement. It should be noted that these patients presenting with involvement of just one organ system often went on to develop combined respiratory and gastrointestinal disease after the time of enrollment.

Table IV also lists the mean ages at zero time for patients in the groups defined by symptoms clusters. (In each case the median ages are quite similar to the means.) Patients with meconium ileus were enrolled by two months of age, and those with isolated steatorrhea were enrolled by an average age of just a year and a half. In contrast, patients with combined respiratory and gastrointestinal disease were enrolled at an average of three and a half years of age, and those with respiratory disease alone at six years of age.

5. Interval between birth and the onset of respiratory symptoms: Upon the advice of several clinicians, we sought associations between the interval from birth to the onset of respiratory symptoms and subsequent clinical outcomes. Table V displays the distribution of patients into groups defined by these intervals. Of the 49 patients with respiratory disease at zero time, 21 had onset of respiratory disease after a year of age. Some of the patients with no respiratory symptoms at zero time may well have developed respiratory disease by three or twelve months of age but were enrolled earlier. The data simply indicate that at the time of enrollment these patients had no respiratory disease.

B. Profile of Clinical Status at Zero Time and Follow-up

To provide a baseline of comparison for the analysis section, a profile of clinical outcomes for the entire cohort has been presented in Table VI. Interestingly, the number of patients with "excellent" scores actually increased over five years, from 34 to 38. Eighteen of the 38 patients with "excellent" scores at five years did not have "excellent" scores at enrollment and thus improved in clinical category over five years. The median total Shwachman score rose slightly from 88 to 89. As indicated by the table, just 25 of 89 patients (28%) deteriorated in clinical category over five years while 64 of 89 (72%) were stable. Of the latter, 42 remained in the same category while 22 actually improved in clinical category. These data indicate that after five years, the cohort had relatively stable scores with a substantial number of patients actually improving. It must be noted, however, that the number of patients in the "terminal" category increased from zero at entry to five at follow-up, with four of these representing deaths. The survival rate was 96%. Hence, despite the overall improvement in the cohort, some patients deteriorated substantially.

C. Analysis

The overall goal of this analysis is to identify associations between clinical features apparent at zero time and subsequent clinical courses. Outcomes have been measured in terms of changes in clinical category relative to a baseline zero time status. To make the change in status more meaningful, we have presented the clinical scores at zero time as well as the subsequent changes in clinical category. This analysis section has been organized so as to clearly distinguish between features associated with poor scores at

zero time and those associated with distinct changes in status over follow-up intervals.

1. Clinical features associated with poor baseline status but not associated with distinctive changes in clinical category:

a). Clubbing: The data in Table VII indicate that patients with mild or moderate clubbing had proportionally fewer "excellent" scores at zero time than patients with no evidence of clubbing. Furthermore, 25% of patients with moderate to severe clubbing had "poor" scores compared to 1% among the rest of the cohort. Hence, clubbing denotes a poor clinical status when patients are first enrolled in the clinic. However, as evidenced by the table, clubbing does not predict distinctive differences in the clinical course after five years.

b). Pseudomonas culture results: Similar to clubbing, positive throat cultures for pseudomonas were associated with proportionally fewer "excellent" and more "poor" scores than in the rest of the cohort. Again, however, the five year follow-up data revealed that positive cultures were not associated with distinctive changes in clinical category.

2. Clinical features associated with distinctive changes in clinical category after five years, but not with distinctive scores at zero time:

a). Co-morbidity: It should be noted that only six patients in the cohort had co-morbid disease at presentation. At zero time both patients with co-morbidity and those without co-morbidity had comparable clinical scores. However, after five years of follow-up, the six patients with co-morbidity had greater deterioration in clinical category than the rest of the cohort. Because of the small number of patients with co-

morbidity, the result is not statistically significant ($P > .10$). (Note that P values are two tailed in this study). Therefore, the prognostic effect of co-morbidity at five years is unclear.

3. Clinical features grouped according to organ system involvement: Outcomes in the four principal groups of patients defined by organ system involvement are displayed in Table IX-A. The fifth group, comprised of patients diagnosed on the basis of a positive family history and found to be asymptomatic, consisted of just two individuals. Because this group was so small, it was excluded from the analysis. The courses of these two patients were typical of the group as a whole. One had zero time and five year scores of 90 and 85, respectively. The other had scores of 94 and 89.

The association between organ system involvement and five year outcomes (Table IX) was statistically significant ($X^2 = 7.8$; $P = .05$). Analysis of the four principal groups indicates that patients presenting with steatorrhea only had the most stable clinical courses at five year follow-up, with just two of 22 (8%) deteriorating in clinical category. In fact, while 11 patients in this group had "excellent" scores at zero time, 17 had excellent scores at five years. This observation indicates that, with some frequency, the status of patients with steatorrhea can be expected to improve over the first five years of follow-up. Patients with gastrointestinal and respiratory disease had the next best outcomes, with 29 of 41 (71%) stable over five years. It should be noted, however, that these patients have the poorest scores at enrollment with only 9 of 41 (22%) in the "excellent" category and four (10%) with "poor" scores at zero time. Patients with meconium ileus had third best clinical outcomes with seven of 14 (50%)

stable. Interestingly, the presence or absence of peritonitis and resection did not affect the results. Finally, patients presenting with isolated respiratory disease had the best zero time scores but the most deterioration at five year follow-up, with four of eight (50%) dropping in clinical category. With so few patients in the group, the result is not statistically persuasive; hence, the actual prognostic significance of the poor outcomes in patients with isolated respiratory disease is difficult to assess from our data.

A multivariate analysis was performed to determine whether the strong association between organ system involvement and subsequent outcomes persisted when potentially confounding variables were held constant. The SAS multivariate program was used. Our results revealed that at five years the association remained statistically significant, even when gender, clubbing, and co-morbidity were added to the multiple regression.

In general, the data reveal that the 49 patients with respiratory disease had worse post-zero time courses than patients who presented with gastrointestinal disease. We sought clinical features which could separate these patients with respiratory disease into prognostically distinct subgroups. The presence vs. absence of gastrointestinal diseases did not satisfactorily differentiate the patients because the group with isolated respiratory disease numbered just eight, too few for statistically meaningful analysis. Based on the advice of several clinicians, we employed the following features to distinguish among patients with respiratory disease: The anatomic site of disease, the initial chest x-ray score, the interval between birth and the onset of respiratory symptoms and the results of initial staph aureus cultures. The results of these subgroupings are displayed in Tables IX-B-E and are discussed below.

a). Anatomic site of respiratory disease: Patients with respiratory symptoms were categorized in the "alveolar" group if they presented with pneumonitis or a history of at least two episodes of pneumonia, and in the "upper airway" group if they did not have alveolar involvement. Five year follow-up data indicate that substantially more patients with "alveolar" disease deteriorated than those with upper airway disease. Although the numbers are small and the results do not achieve conventional levels of statistical significance ($X^2 = 1.55$, $P = .21$), the clinical trend is impressive.

b). Initial chest x-ray score: Patients were separated into two groups on the basis of the chest x-ray component of their total Shwachman scores. As discussed in the Methods section, the x-ray score was assigned by the method of Brasfield et al.[23] with maximum score being 25. One group had x-ray scores less than or equal to 21; the other group had scores greater than 21. Not surprisingly, the patients with x-ray scores of 21 or less had much worse zero time scores. Interestingly, however, the initial x-ray score had no association with subsequent change in clinical status. Hence, the finding of a chest x-ray score of 21 or less is a marker for poor status at zero time but does not help to identify patients who will deteriorate over follow-up intervals.

c). Interval between birth and the onset of respiratory symptoms: Patients were divided into two groups defined by the interval between birth and the onset of respiratory symptoms. Five year follow-up data indicated substantially greater deterioration in the scores of patients with the onset of respiratory disease before three months of age in the scores of patients with onset of disease after three months of age.

d). Staph aureus culture results: The results of initial cultures for staph aureus did not distinguish among the five year courses of patients presenting with respiratory disease.

In sum, these sub-stratifications suggest that among patients presenting with respiratory disease, two zero time findings identified groups of children with substantially greater deterioration after five years. These included the presence of alveolar disease and a history of respiratory symptoms beginning before three months of age. The results of staph aureus cultures and the initial chest x-ray score were not associated with distinctive patterns of clinical deterioration after five years, although as expected the lower chest film scores were associated with worse zero time status.

From the data presented thus far, three broad group of patients emerge with distinct five year courses: Patients presenting with steatorrhea have markedly stable five year courses; those with respiratory disease which was either alveolar and/or occurred before three months of age had distinctively poor outcomes; patients presenting with meconium airways and/or occurring after three months of age had intermediate outcomes after five years.

e). Activity score as measures of outcome: The preceding paragraphs indicate that respiratory disease was associated with poor outcomes. One could argue that the Shwachman score is heavily weighted toward respiratory disease, and therefore that the results are simply tautologous. In fact, we feel that the Shwachman system provides a balanced assessment of clinical status. Nevertheless, we have examined outcomes in terms of activity scores, a global rather than organ-specific measure of clinical status.

Activity scores were used to measure the outcomes of patients in the four groups defined by organ system involvement at zero time. Results are displayed in Table IX-F. The activity categories were defined by scores suggested by several clinicians: Excellent = 24-25; good = 21-23; fair = 16-20; and poor = < 15. At five years, the entire cohort had 64 stable outcomes defined by total Shwachman scores and 69 defined by activity score. Results for specific subgroups were similarly analogous (compare with Table IX-A). Overall, it is clear that the results obtained with total Shwachman scores are substantiated by this less organ specific measure of clinical outcome.

4. Clinical features neither associated with distinctive zero time scores nor with distinctive changes in clinical course after five years of follow-up: Table X presents data which document that several of the clinical features we examined were neither associated with distinctive scores at zero time nor with distinctive courses after five years. These features included the initial total Shwachman score, the secular period of enrollment, and the age at zero time. The finding that the initial total Shwachman score was not related to subsequent clinical course is crucial to this study. The result indicates clearly that patients destined to deteriorate fastest are not necessarily those that look worse at enrollment. The study shows that clinical features such as organ system involvement are much more powerful indicators of subsequent clinical course.

III. Results of the Ten Year Cohort

To re-emphasize a point made in the beginning of the Results section, the "ten year" cohort of 55 patients is distinct from the "five year" cohort of 89 patients. In this section the composition of the ten year cohort will

be discussed briefly with emphasis on distinctions between this group and the five year cohort. Results obtained from analysis of the ten year cohort shall be presented as well.

A. Description of the Cohort

Pertinent demographic characteristics of the cohort are displayed in Table XI. Females outnumbered males (29 to 26) whereas in the five year cohort there were 44 females and 45 males. The distribution of ages at zero time was quite similar to that in the five year cohort.

The prevalence of co-morbidity and clubbing at zero time along with initial throat culture results are displayed in Table XII. All six of the patients in the five year cohort who had co-morbidity were enrolled before 1973 and thus were included in the ten year cohort as well. Hence, there is proportionally more co-morbidity in the ten year cohort. The proportion of patients with actual nailbed swelling (moderate to severe clubbing) is slightly lower in the ten year cohort than in the five year group. The same is true of positive cultures for pseudomonas at zero time, while the proportion of patients with positive cultures for staph was actually higher in the ten year group. In general, with the exception of co-morbidity, the composition of the two cohorts did not differ substantially.

Table XIII displays the symptoms at zero time in the ten year cohort. The two groups were similarly composed with respect to respiratory and gastrointestinal symptoms. The representation of patients in groups defined by clusters of symptoms was similar in the two cohorts as well, as evidenced by the data in Table XIV. Table XV displays the interval from birth to the onset of respiratory symptoms for the patients in the cohort enrolled before 1973. The data indicate that the two cohorts were similar, with minor

differences. For example, 22 of 55 (40%) patients in the ten year cohort reported onset of respiratory symptoms before one year of age, compared with 27 of 89 (30%) of the five year cohort.

B. Profile of Clinical Status at Follow-up

Table XVI provides a profile of clinical outcomes for the ten year cohort. The zero time scores of the group enrolled before 1973 were similar to those of the larger cohort (compare with Table VI). However, after ten years of follow-up, the number of patients with excellent scores decreased by a third, while 14 patients, or a quarter of the cohort, had poor or terminal scores. Five of these represented deaths. The ten year survival rate was 91%. The extent of clinical deterioration is also indicated in Table XVI which shows that 25 of 55 (45%) patients in the cohort had clinical deterioration after ten year.

IV. Analysis

A. Clinical Features Associated With Distinctive Clinical Outcomes at Ten Year Follow-up

Analysis of gender revealed that females had markedly greater deterioration in scores than males after ten years of follow-up (Table XVII-A). While the result is not statistically significant ($P = .15$) the trend is impressive. This finding that females deteriorate at around ten years after diagnosis is consistent with previously reported data. Table XVII-B reveals that positive cultures for staph aureus were associated with significant deterioration in clinical status after ten year ($X^2 = 4.9$, $P < .05$). Recall that in the five year cohort, positive cultures for staph were neither associated with distinct zero time scores nor with distinct five year follow-up courses.

B. Clinical Features Associated With Distinctive Outcomes at Zero Time and at Ten Year Follow-up

1. Clubbing: In the five year cohort, clubbing was associated with poor zero time scores but not with distinctive outcomes after five years of follow-up. In contrast, the data in Table XVIII-A suggest that the presence of clubbing, especially moderate to severe, was associated with deterioration in scores after ten years. The result was not statistically significant ($X^2 = 2.4$, $P = .10$). Two observations cast doubt on the importance of the clinical trend noted. First, the number of patients in the ten year cohort is small. Furthermore, comparison with Table VII reveals that the clubbed patients in the ten year cohort are disproportionately represented by patients who had already deteriorated by five years.

2. Organ system involvement: The ten year outcomes of patients stratified by organ system involvement are displayed in Table XVIII. The association between organ system involvement and ten year outcomes was not statistically significant ($X^2 = 4.9$; $P = 0.18$). However, the clinical trend is impressive and is similar to the results of the five year group. Once again, patients with steatorrhea only had the most stable courses, with ten of 14 (71%) having stable outcomes after ten years. Patients with combined gastrointestinal and respiratory disease had the next best outcomes with 16 of 27 (59%) stable after ten years. Patients with meconium ileus and those with isolated respiratory disease at zero time had the worst ten year courses, with only around 30% of patients in each group stable. It should be noted, however, that the size of both groups is small. As was noted in

the five year cohort, the presence of peritonitis or resection had no bearing on the outcomes of patients with meconium ileus.

Multivariate analysis showed that the impressive though not statistically significantly relationship between organ system involvement and ten year course remained impressive when such potentially confounding factors as gender, co-morbidity, and clubbing were entered into the analysis.

As in the five year analysis, we have sub-stratified patients in the ten year cohort who presented with respiratory disease. The data reveal that the anatomic site of pathology did not differentiate patients in the ten year cohort into prognostically distinct groups. However, it should be noted that the cohort includes only eight patients with alveolar disease. The initial chest x-ray score had no bearing on the clinical course after ten years of follow-up. In contrast, both onset of respiratory symptoms before three months of age and a positive initial culture for staph aureus were associated with significantly greater deterioration in clinical status after ten years.

An interesting finding emerges when patients presenting with respiratory disease are stratified by gender. Of the 15 males in the ten year cohort who presented with respiratory symptoms, nine (69%) had stable courses after ten years. In contrast, of 20 females, only nine (45%) had stable ten year courses. Hence, females with respiratory disease had more deterioration over ten years than the males. While the numbers are not statistically significant, they are impressive. This pattern was not evidence at five years in the five year cohort. The result is consistent with previously reported claims that females deteriorate faster than males in the teen age years.[24]

Another result also aids in understanding why females appeared to fare worse than males in the cohort. It turns out that ten of 14 (71%) patients presenting with steatorrhea were males. Males and females in the group fared equally well. In contrast, 20 of 30 (61%) patients with respiratory disease were females. While females with respiratory disease clearly did worse than males, some of the difference in outcome between males and females in the cohort must be attributed to the disproportionate representation of males in the prognostically favorable group with steatorrhea only.

In sum, as in the five year cohort, three groups can be defined with distinct outcomes after ten years. Patients with steatorrhea only in general do well. Patients with respiratory disease do worse. Subgroups of patients presenting with respiratory disease who have particularly poor outcomes include females, patients with positive initial cultures for staph aureus, and patients with early onset of respiratory disease. These results differ from those obtained at five years in the five year cohort in that a positive culture for staph and female gender had no association with distinctive five year outcomes in the five year cohort.

3. Clinical features not associated with distinct outcomes at zero time nor at ten year follow-up: The age at zero time and the initial total Shwachman score were not associated with distinctive outcomes at ten years of follow-up. Those features had no bearing on outcomes in the five year cohort either. Co-morbidity was not associated with distinctive ten year outcomes, although in the five year cohort co-morbidity was associated with deterioration in clinical course. The discrepancy could be due at least in part to the small number of patients with co-morbidity (6) in the study.

TABLE 1

Demographic Characteristics at Zero Time (N=89)

Characteristic	N	(%)
Gender		
Male	45	(51)
Female	44	(49)
Race		
White	87	(98)
Black	2	(2)
Hispanic	0	(0)
Number of Siblings with Cystic Fibrosis		
None	77	(87)
One	9	(10)
Two or more	3	(3)
Age		
3 months	23	(26)
3 to 12 months	19	(21)
1 to 3 years	23	(26)
3 to 7 years	15	(17)
7 to 10 years	4	(4)
10 years	5	(6)
Secular Period of Enrollment		
1966 - 1969	23	(26)
1970 - 1972	22	(25)
1973 - 1975	24	(27)
1976 - 1978	20	(22)

TABLE 2

Select Clinical Features at Zero Time (N=89)

Clinical Feature	N	(%)
Co-morbidity		
None	83	(93)
Prematurity (4 weeks pre-dates)	3	(3)
Neonatal Sepsis (includes one case of respiratory distress synd)	3	(3)
Clubbing		
Absent	69	(77)
Mild (erythema)	8	(9)
Moderate to severe (nail bed swelling)	12	(14)
Results of Initial Throat Cultures for Staph Aureus		
Not Cultured	2	(2)
Positive	26	(29)
Negative	61	(69)
Results of Initial Throat Cultures for Pseudomonas Aeruginosa		
Not cultured	2	(2)
Positive	11	(13)
Negative	76	(85)

TABLE 3

Symptoms at Zero Time (N=89)

Symptoms	N	(%)
Respiratory		
Alveolar*	17	(19)
Upper airway, without alveolar+	32	(36)
None	40	(45)
Gastrointestinal		
Meconium ileus		
Without resection or peritonitis	9	(10)
With resection and/or peritonitis	5	(6)
Steatorrhea#	65	(73)
None	10	(11)

* "Alveolar" includes history of two or more episodes of pneumonia or acute pneumonitis at zero time.

+ "Upper airway" includes history of chronic cough, wheezing, or two or more episodes of bronchitis.

# "Steatorrhea" includes bulky, foul smelling stools; rectal prolapse; abdominal pain; and constipation.

TABLE 4

Clusters of Symptoms at Enrollment (N=89)

Symptom Cluster	N	(%)	Age at Zero Time (months)
Family history, asymptomatic	2	(2)	
Meconium ileus	14	(16)	2 ± 1
Steatorrhea	24	(27)	19 ± 20
Gastrointestinal plus Respiratory	41	(46)	43 ± 58
Respiratory only	8	(9)	73 ± 64

TABLE 5

Interval from Birth to the Onset of Respiratory Symptoms (N=89)

Interval	N	(%)
0 to <3 months	15	(17)
3 to <12 months	13	(14)
> 1 year	21	(24)
No respiratory symptoms at zero time	40	(46)

TABLE 6

Profile of Clinical Outcomes (N=89)

Total Shwachman Scores at Enrollment and at Five Year Follow-up:

Time	Clinical Status					
	Excellent	Good	Fair	Poor	Terminal*	Total
Enrollment	34 (38%)	44 (49%)	7 (8%)	4 (4%)	0 (0%)	89
Five year follow-up	38 (43%)	35 (39%)	9 (10%)	2 (2%)	5 (6%)	89

*Five terminal patients at five year follow-up included four deaths

Change in Clinical Category at Five Year Follow-up:

Follow-up	Stable*	Deteriorating+	Total
Five years	64 (72%)	23 (28%)	89

* Stable refers to patients whose clinical category improved or remained the same.

+ Deteriorating refers to patients who have dropped to a lower clinical category.

TABLE 7

Clinical Features Associated with Distinctive Outcomes at Zero Time but not with Distinctive Changes in Clinical Category (N=89)

Clubbing

Clubbing Status	Clinical Status at Zero Time Excellent	Good	Fair	Poor	Terminal	Totals
Absent	31 (45%)	31 (45%)	6 (9%)	1 (1%)	0 (0%)	69
Mild	1 (12%)	7 (88%)	0 (0%)	0 (0%)	0 (0%)	8
Moderate to Severe	2 (17%)	6 (50%)	1 (8%)	3 (25%)	0 (0%)	12
Totals	34 (38%)	44 (49%)	7 (8%)	4 (4%)	0 (0%)	89

Clubbing Status	Five Year Status Stable	Deteriorating	Totals
Absent	51 (74%)	18 (26%)	69
Mild	5 (63%)	3 (37%)	8
Moderate to Severe	8 (67%)	4 (33%)	12
Totals	64 (72%)	25 (28%)	89

Pseudomonas Culture Results

Culture Status	Clinical Status at Zero Time Excellent	Good	Fair	Poor	Terminal	Totals
Not cultured	0 (0%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2
Positive	1 (9%)	7 (64%)	1 (9%)	2 (18%)	0 (0%)	11
Negative	33 (43%)	35 (46%)	6 (8%)	2 (3%)	0 (0%)	76
Totals	34 (38%)	44 (49%)	7 (8%)	4 (4%)	0 (0%)	89

Culture Status	Five Year Status Stable	Deteriorating	Totals
Not Cultured	2 (100%)	0 (0%)	2
Positive	7 (64%)	4 (36%)	11
Negative	55 (72%)	21 (28%)	76
Totals	64 (72%)	25 (28%)	89

TABLE 8

Clinical Features Associated with Distinctive Changes in Clinical Category after Five Years, but not with Distinctive Zero Time Outcomes (N=89)

Co-morbidity

Co-morbid Status	Excellent	Good	Fair	Poor	Terminal	Totals
	Clinical Status at Zero Time					
Co-morbidity Present	2 (33%)	3 (50%)	1 (17%)	0 (0%)	0 (0%)	6
Co-morbidity Absent	32 (39%)	41 (49%)	6 (7%)	4 (5%)	0 (0%)	83
Totals	34 (38%)	44 (49%)	7 (8%)	4 (4%)	0 (0%)	89

Co-morbid Status	Five Year Status		
	Stable	Deteriorating	Totals
Co-morbidity Present	3 (50%)	3 (50%)	6
Co-morbidity Absent	61 (73%)	22 (27%)	83
Totals	64 (72%)	25 (28%)	89

TABLE 9

Clinical Features Associated with Distinctive Outcomes Both at Zero Time and at Five Year Follow-up (N = 87)

A. Organ System Involvement

Organ System	Clinical Status at Zero Time					
	Excellent	Good	Fair	Poor	Terminal	Totals
Steatorrhea	11 (46%)	11 (46%)	2 (8%)	0 (0%)	0 (0%)	14
Gastrointest and Respir	9 (22%)	24 (59%)	4 (10%)	4 (10%)	0 (0%)	41
Meconium ileus	7 (50%)	6 (43%)	1 (7%)	0 (0%)	0 (0%)	14
Respiratory alone	5 (62%)	3 (38%)	0 (0%)	0 (0%)	0 (0%)	8
Totals	32 (37%)	44 (51%)	7 (8%)	4 (5%)	0 (0%)	87

Organ System	Five Year Status			
	Stable	Deteriorating	Totals	Deaths
Steatorrhea	22 (92%)	2 (8%)	14	1
Gastrointest and Respir	29 (71%)	12 (29%)	41	2
Meconium ileus	9 (64%)	5 (36%)	14	1
Respiratory alone	4 (50%)	4 (50%)	8	1
Totals	64 (73%)	23 (26%)	87	4

B. Site of Respiratory Disease

Site	Five Year Status		
	Stable	Deteriorating	Totals
Alveolar	9 (53%)	8 (47%)	17
Upper Airway	24 (75%)	8 (25%)	32
Totals	33 (67%)	16 (33%)	49

TABLE 9, continued

C. Initial Chest X-Ray Score

	Clinical Status at Zero Time					
Score	Excellent	Good	Fair	Poor	Terminal	Totals
less than or =21	2 (7%)	17 (63%)	4 (15%)	4 (15%)	0 (0%)	27
greater than 21	12 (55%)	10 (45%)	0 (0%)	0 (0%)	0 (0%)	22
Totals	14 (29%)	27 (55%)	4 (8%)	4 (8%)	0 (0%)	49

	Five Year Status		
Score	Stable	Deteriorating	Totals
less than or =21	18 (67%)	9 (33%)	27
greater than 21	15 (68%)	7 (32%)	22
Totals	33 (67%)	16 (33%)	49

D. Interval from Birth to the Onset of Respiratory Symptoms

	Five Year Status		
Interval	Stable	Deteriorating	Totals
less than 3 months	8 (53%)	7 (47%)	15
greater than or = 3 months	24 (73%)	9 (27%)	33
Totals	32 (67%)	16 (33%)	48

E. Results of Initial Cultures for Staph Aureus

	Five Year Status		
Results	Stable	Deteriorating	Totals
Positive	11 (65%)	6 (35%)	17
Negative	22 (69%)	10 (31%)	32
Totals	33 (67%)	16 (33%)	49

TABLE 9, continued

F. Association Between Organ System Involvement and Changes in Activity Category over Five Years (N = 87)

Organ System	Five Year Activity Status Stable		Deteriorating		Total
Steatorrhea	23	(96%)	1	(4%)	24
Gastrointest and Respir	32	(78%)	9	(22%)	41
Meconium ileus	10	(71%)	4	(29%)	14
Respiratory alone	4	(50%)	4	(50%)	8
Totals	69	(79%)	18	(21%)	87

Stable: Activity category improves or remains the same.

Deteriorating: Activity category worsens over the interval of follow-up.

Activity Categories: Excellent = 24-25; Good = 21-23; Fair = 16-20; Poor = less than 16.

TABLE 10

Clinical Features Neither Associated With Distinctive Zero Time Scores nor With Distinctive Changes in Clinical Category after Five Years (N = 89)

A. Secular period of enrollment

Secular Period	Clinical Status at Zero Time					
	Excellent	Good	Fair	Poor	Terminal	Total
1966-72	19 (42%)	22 (49%)	2 (4%)	2 (4%)	0 (0%)	45
1973-78	15 (34%)	22 (50%)	5 (11%)	2 (5%)	0 (0%)	44
Totals	34 (38%)	44 (49%)	7 (8%)	4 (4%)	0 (0%)	89

Secular Period	Five Year Status		
	Stable	Deteriorating	Totals
1966-72	31 (69%)	14 (31%)	45
1973-78	33 (75%)	11 (25%)	44
Totals	64 (72%)	25 (28%)	89

B. Age at Zero Time

Age	Clinical Status at Zero Time					
	Excellent	Good	Fair	Poor	Terminal	Total
≤3 months	12 (52%)	10 (43%)	1 (4%)	0 (0%)	0 (0%)	23
>3 - 12 mon.	8 (42%)	6 (32%)	4 (21%)	1 (5%)	0 (0%)	19
>12-36 mon.	6 (26%)	17 (74%)	0 (0%)	0 (0%)	0 (0%)	23
>36 months	8 (33%)	11 (46%)	2 (8%)	3 (12%)	0 (0%)	24
Totals	34 (38%)	44 (49%)	7 (8%)	4 (4%)	0 (0%)	89

Age	Five Year Status		
	Stable	Deteriorating	Totals
≤ 3 months	14 (61%)	9 (39%)	23
> 3-12 months	13 (68%)	6 (32%)	19
> 12-36 months	20 (87%)	3 (13%)	23
≥ 36 months	17 (71%)	7 (29%)	24
Totals	64 (72%)	25 (28%)	89

TABLE 10, continued

C. Initial Total Shwachman Score

	Five Year Status		
Score	Stable	Deteriorating	Totals
90 - 100 (excellent)	20 (59%)	14 (41%)	34
80 - 89 (good)	35 (79%)	9 (21%)	44
79 (fair, poor)	9 (82%)	2 (18%)	11
Totals	64 (72%)	25 (28%)	89

D. Gender

	Clinical Status at Zero Time					
Gender	Excellent	Good	Fair	Poor	Terminal	Totals
Male	17 (38%)	21 (47%)	4 (9%)	3 (7%)	0 (0%)	45
Female	17 (39%)	23 (52%)	3 (7%)	1 (2%)	0 (0%)	44
Totals	34 (38%)	44 (49%)	7 (8%)	4 (4%)	0 (0%)	89

	Five Year Status		
Gender	Stable	Deteriorating	Totals
Male	33 (73%)	12 (27%)	45
Female	31 (70%)	13 (30%)	44
Totals	64 (72%)	25 (28%)	89

E. Staph Aureus Results

	Clinical Status at Zero Time					
Culture Status	Excellent	Good	Fair	Poor	Terminal	Totals
Not cultured	0 (0 %)	2 (100%)	0 (0 %)	0 (0%)	0 (0%)	2
Positive	9 (35%)	12 (46%)	4 (15%)	1 (4%)	0 (0%)	26
Negative	25 (41%)	30 (49%)	3 (5%)	3 (5%)	0 (0%)	61
Totals	34 (38%)	44 (49%)	7 (8%)	4 (4%)	0 (0%)	89

	Five Year Status		
Culture Status	Stable	Deteriorating	Totals
Not cultured	2 (100%)	0 (0%)	2
Positive	19 (73%)	7 (27%)	26
Negative	43 (70%)	18 (30%)	61
Totals	64 (72%)	25 (28%)	89

TABLE 11

Demographic Features at Zero Time (N=55)

Feature	N	(%)
Gender		
Male	26	(47)
Female	29	(53)
Age		
< 3 months	13	(24)
3 to < 12 months	13	(24)
1 to < 3 years	15	(27)
3 to < 7 years	9	(16)
7 to < 10 years	3	(5)
≥ 10 years	2	(4)

TABLE 12

Select Clinical Features at Zero Time (N=55)

Feature	N	(%)
Co-morbidity		
None	49	(89)
Prematurity (4 weeks pre-dates)	3	(5)
Neonatal Sepsis (includes one case respiratory distress syndrome)	3	(5)
Clubbing		
Absent	45	(82)
Mild (erythema)	5	(9)
Moderate to Severe (nailbed swelling)	5	(9)
Results of Initial Throat Cultures for Staph Aureus		
Not cultured	1	(2)
Positive	18	(33)
Negative	36	(65)
Results of Initial Throat Cultures for Pseudomonas		
Not Cultured	1	(2)
Positive	5	(10)
Negative	49	(89)

TABLE 13

Symptoms at Zero Time (N=55)

Symptom	N	(%)
Respiratory		
Alveolar	8	(15)
Upper Airway	25	(46)
None	22	(40)
Gastrointestinal		
Meconium ileus		
Without resection or peritonitis	3	(5)
With resection or peritonitis	4	(7)
Steatorrhea	41	(74)
None	7	(13)

TABLE 14

Clusters of Symptoms at Zero Time (N=55)

Symptom Cluster	N	(%)
Family history, asymptomatic	1	(2)
Meconium ileus	7	(13)
Steatorrhea	14	(25)
Gastrointestinal and Respiratory	27	(48)
Respiratory only	6	(11)

TABLE 15

Interval from Birth to the Onset of Respiratory Symptoms

(N=55)

Interval	N	(%)
0 to < 3 months	12	(22)
3 to < 12 months	10	(18)
> 1 year	10	(18)
No respiratory symptoms at zero time	23	(42)

TABLE 16

Profile of Clinical Outcomes (N = 55)

Total Shwachman Scores

	Clinical Status					
Period	Excellent	Good	Fair	Poor	Terminal	Total
Zero Time	23 (42%)	26 (47%)	4 (7%)	2 (4%)	0 (0%)	55
Ten Years	16 (29%)	19 (35%)	6 (11%)	6 (11%)	8 (15%)*	55

* 8 terminal patients include 5 deaths

Change in Clinical Category at Ten Year Follow-up

Period	Stable	Deteriorating	Totals
Ten years	30 (55%)	25 (45%)	55

TABLE 17

Clinical Features Associated with Distinctive Clinical Outcomes at Ten Year Follow-up (N=55)

Gender

Gender	Ten Year Status Stable	Deteriorating	Totals
Male	17 (65%)	9 (35%)	26
Female	13 (45%)	16 (55%)	29
Totals	30 (55%)	25 (45%)	55

Results of initial cultures for staph aureus

Culture Result	Ten Year Status Stable	Deteriorating	Totals
Positive	7 (39%)	11 (61%)	18
Negative	22 (61%)	14 (39%)	36
Totals	29 (55%)	25 (45%)	54*

* one not cultured

TABLE 18

Clinical Features Associated with Distinctive Outcomes at Zero Time and at Ten Year Follow-up (N = 55)

A. Clubbing

Clubbing Status	Ten Year Status		Totals
	Stable	Deteriorating	
Absent	27 (60%)	18 (40%)	45
Mild	2 (40%)	3 (60%)	5
Moderate to Severe	1 (20%)	4 (80%)	5
Totals	30 (55%)	25 (45%)	55

B. Organ System Involvement

Organ System	Ten Year Status		Totals
	Stable	Deteriorating	
Steatorrhea	10 (71%)	4 (71%)	14
Gastrointest and Resp	16 (59%)	11 (41%)	27
Meconium ileus	2 (29%)	5 (71%)	7
Respiratory alone	2 (33%)	4 (67%)	6
Totals	30 (56%)	24 (44%)	54*

* one in the family history, asymptomatic group

C. Site of Respiratory Disease

Site	Ten Year Status		Totals
	Stable	Deteriorating	
Alveolar	4 (50%)	4 (50%)	8
Upper Airway	14 (56%)	11 (44%)	25
Totals	18 (55%)	15 (45%)	33

TABLE 18, continued

D. Initial Chest X-Ray Score

		Ten Year Status	
Score	Stable	Deteriorating	Totals
less than or = 21	8 (57%)	6 (43%)	14
greater than 21	10 (53%)	9 (47%)	19
Totals	18 (55%)	15 (45%)	33

E. Results of Initial Culture for Staph aureus

		Ten Year Status	
Culture Result	Stable	Deteriorating	Totals
Positive	3 (25%)	9 (75%)	12
Negative	15 (72%)	6 (28%)	21
Totals	18 (55%)	15 (45%)	33

F. Interval Between Birth and the Onset of Respiratory Symptoms

Interval	Stable	Deteriorating	Totals
less than 3 mo.	4 (33%)	8 (67%)	12
greater than or = 3 mo.	14 (67%)	7 (33%)	21
Totals	18 (55%)	15 (45%)	33

G. Gender

		Ten Year Status	
Gender	Stable	Deteriorating	Totals
Male	9 (69%)	4 (31%)	13
Female	9 (45%)	11 (55%)	20
Totals	18 (55%)	15 (45%)	33

TABLE 19

Clinical Features not Associated with Distinctive Outcomes at Zero Time nor at Ten Year Follow-up (N=55)

Age at Zero Time

Age	Stable	Ten Year Status Deteriorating	Totals
≤ 3 months	4 (31%)	9 (69%)	13
> 3 to 12 months	7 (54%)	6 (46%)	13
>12 to 36 months	12 (80%)	3 (20%)	15
> 36 months	7 (50%)	7 (50%)	14
Totals	30 (55%)	25 (45%)	55

Initial Total Shwachman Score

Score	Stable	Ten Year Status Deteriorating	Totals
90 - 100	10 (43%)	13 (52%)	23
80 - 89	16 (61%)	10 (39%)	26
≤ 79	4 (67%)	2 (33%)	6
Totals	30 (55%)	25 (45%)	55

Co-morbidity

Co-morbid Status	Stable	Ten Year Status Deteriorating	Totals
Co-morbidity present	3 (50%)	3 (50%)	6
Co-morbidity absent	27 (55%)	22 (45%)	49
Totals	30 (55%)	25 (45%)	55

DISCUSSION

This concluding chapter is divided into three sections. First, major findings of the study will be discussed with emphasis on the concordance of our results with previously reported data. It should be emphasized that ours is the first study of the clinical features of presentation to focus on morbidity outcomes. Other series have considered only mortality. While it is informative to check our morbidity data against previously noted mortality trends it should be recognized that these two outcomes are distinct. The second section of this chapter will discuss implications of our findings for clinical management and research. Finally, new direction will be suggested for future research on the associations between clinical features of presentation and subsequent outcomes.

I. Major Findings

A. Descriptive Data

The patients entered into the study were generally similar in demographic and clinical features to those followed by other investigators. However, it should be noted that no other authors have examined several of the zero time features considered in this study such as clubbing, co-morbidity, and initial throat culture results. Only two other authors have subgrouped patients according to organ system involvement (Kraemer et al.[9] who studied 204 patients in Berne, Switzerland, and Gurwitz et al.[30] who studied 734 patients followed in Toronto). In general, the distribution of patients in these studies into groups defined by organ system was similar to the distribution in the present study. There were a few differences which merit discussion. Kraemer et al. reported that 7% of patients belonged

in the "family history" category, while the present study included just two patients (2%) in the "family history, asymptomatic" group. As discussed in the Methods sections, our criteria for classification of patients was based on symptom status at zero time. Hence, we included under "family history, asymptomatic" only those patients truly found to have no symptoms. In contrast, while the Kraemer study also purports to focus on symptom status at presentation, their classification is based on the stimulus for diagnosis -- the family history -- without regard for actual symptom status of patients in this group. We considered performing a separate analysis of the prognostic significance of various diagnostropic stimuli, but were unable to assemble sufficiently reliable data.

The distribution of males and females into groups defined by organ system involvement also differed considerably in our group from previously reported findings. Gurwitz et al. reported on 734 patients and found that the numbers of males and females in groups defined by organ system were roughly equal. Specifically, among 121 patients presenting with steatorrhea only, 52% were male. Also, 52% of 515 patients with respiratory disease (either isolated or occurring with steatorrhea at zero time) were male. In contrast, we found that of 24 patients in the five year group presenting with steatorrhea 58% were male. Also, of 49 patients in our overall cohort presenting with respiratory disease, just 41% were male. Hence, in our study, the most prognostically favorable group (steatorrhea alone) was disproportionately represented by males, and the least prognostically favorable groups (respiratory disease) were disproportionately represented by females. Because our cohort is much smaller than the Gurwitz series, it

is possible that our results could represent sampling artifact rather than a true clinical distinction.

A final area in which our cohort differed from previously reported groups was the age at presentation. Kraemer et al. report that patients with isolated respiratory disease had an average age of 21 months at presentation, and those with combined respiratory and gastrointestinal disease an average of 27 months. Corresponding values for our study were 73 (± 64) months for isolated respiratory symptoms and 43 (± 58 months) for combined respiratory disease and steatorrhea. Several reasons can be offered to explain these differences. It is possible that the earlier age of diagnosis in the Kraemer series reflects heightened suspicion of CF on the part of physicians. This is unlikely in view of the fact that the Kraemer study includes patients diagnosed in the 1950's when the level of clinical suspicion of cystic fibrosis was probably lower. The difference could also be due to different biologic behavior of the diseases in Europe than in the U.S. No data exist to support this hypothesis. More likely, our series includes patients whose symptoms did not become severe enough to raise the suspicion of CF until a relatively late age. These patients might have been missed at an earlier secular period when the disease was regarded as more homogeneous in expression, with symptoms appearing in infancy. The significance of late manifestations of CF has been discussed in the literature,[6] but remains poorly understood. The patients could represent a milder variant of CF with the manifestations remaining subclinical until relatively late. Alternatively, these patients could have a variant which is no less severe than usual but is expressed in later years.

B. Mortality Data

The survival in the five year cohort was 96%; in the ten year cohort, survival was 91%. These figures are comparable to survival data reported by the Cystic Fibrosis Foundation.[3] It is striking that three out of four deaths in the five year group and four out of five in the ten year group occurred in patients presenting with respiratory disease. In fact, the one death in the five year cohort occurring in a patient without respiratory disease (he had meconium ileus) was not primarily due to CF. This patient had an "excellent" total Shwachman score just before death. None of the patients presenting with steatorrhea alone died. All but one of the deaths of patients presenting with respiratory disease occurred in females. There was no distinctive pattern in the ages at diagnosis of patients who died. These data are consistent with the conclusions of Kraemer et al.[9] that steatorrhea alone is associated with the highest five and ten year survival rates, and that the presence of respiratory disease at presentation is associated with lower survival rates.

C. Morbidity Data

This study focused primarily on morbidity, both because death was an infrequent outcome event in our cohorts and because we felt changes in clinical status short of death are critical for patient management and germane to clinical research. Major findings are discussed below:

1. Clinical features associated with poor zero time scores: These included positive culture for pseudomonas and the presence of clubbing. Our results are consistent with generally accepted descriptions of the progression of CF[4] in which clubbing and pseudomonas colonization are felt to occur initially in patients with relatively poor overall status.

Interestingly, the patients with clubbing and pseudomonas colonization at zero time do not deteriorate in clinical status any faster than the rate of the cohort as a whole. This observation indicates that clinical markers of advanced disease do not necessarily signal impending deterioration.

2. Organ system involvement: The association between organ system involvement and subsequent outcomes was statistically significant in the five year group and impressive though not significant in the ten year group. Multivariate analysis revealed that even when such factors as gender, co-morbidity, and the presence of clubbing were held constant, organ system involvement continued to be strongly associated with distinct outcomes. This is perhaps our most important finding. It affirms the basic hypothesis of the study: That patients can indeed be separated into prognostically distinct groups based on clinical features at presentation. Results of each of the groups will be discussed below.

a). Meconium ileus: The morbidity of patients with meconium ileus were typical of the entire cohort both at zero time and at five years. In contrast, several series, including the Kraemer study, report that meconium ileus was associated with the worst prognosis in terms of mortality.[9] Several reasons explain the better outcomes of patients with meconium ileus in our series. First, other investigators, including Kraemer et al., include only patients requiring surgery in their meconium ileus group, categorizing patients with meconium ileus relieved by gastrograffin enema as "gastrointestinal". Since the bulk of mortality is due to surgery, the Kraemer criteria select for a group more likely to have poor outcomes. We feel our classification is preferable because it is based on the actual presence or absence of intestinal obstruction rather than the success of a

particular therapeutic maneuver, the gastrograffin enema. Meconium ileus also had a more favorable prognosis in our series in part because we did not include patients who died in infancy of small bowel obstruction, thus never enrolling in the Yale clinic. This unavoidable exclusion probably also explains why patients with resection or peritonitis did not do especially poorly in our series. Dire sequelae of these complication probably result in death before patients are enrolled in the clinic. More recent series have reported that patients with meconium ileus have similar courses to those with normal births. Authors have attributed the improved outcomes over the last 15 years to improvements in operative techniques, life support, and management.[2] Hence, the Kraemer series, which included patients enrolled in the 1950's, spans prognostically distinct secular intervals.

b). Steatorrhea: In both the five and ten year cohorts, patients presenting solely with steatorrhea (or related problems such as rectal prolapse) had considerably less morbidity than the rest of the cohort. Our results for morbidity are consistent with the finding of Kraemer et al. in which patients with steatorrhea had the lowest mortality at five and ten year follow-up. These results are also consistent with a widely accepted understanding of the significance of involvement of different organ systems.[2] Gastrointestinal disease can be ameliorated with pancreatic enzymes and does not contribute to mortality or significant morbidity. Patients presenting with steatorrhea are treated with enzymes and become virtually asymptomatic until the onset of respiratory disease. Respiratory involvement, in contrast, progresses insidiously despite therapy. Hence, patients presenting with steatorrhea in a sense "wave a red flag", signalling

their diagnosis at a stage in their disease at which they do not have clinically apparent lung involvement. Whether the respiratory disease that ultimately develops in these patients is as severe as in patients initially presenting with respiratory symptoms is beyond the scope of this study.

c). Respiratory disease: In general, patients with respiratory disease had poor outcomes at follow-up intervals. We suspected this group to be heterogeneous with respect to prognosis, and therefore attempted to identify those clinical features associated with particularly poor outcomes in patients presenting with respiratory disease.

1). Combined respiratory and gastrointestinal disease: Our data suggest that the presence of gastrointestinal disease is associated with a better prognosis than respiratory disease alone. This finding is consistent with the "protective" effect of gastrointestinal disease noted by Kraemer et al. However, there were few patients in our cohorts with isolated respiratory disease. Our results must therefore be interpreted cautiously.

2). Alveolar disease: Patients presenting with alveolar disease had especially poor outcomes after five years of follow-up. The anatomic site of disease has not been considered in previous studies. This trend was not observed at ten year follow-up; however, the number of patients with alveolar disease in the ten year group was small.

3). Onset of disease in the perinatal period: Patients with appearance of respiratory symptoms by three months of age had especially poor outcomes at five and ten years. Our data support the hypothesis that onset of respiratory symptoms early in infancy heralds an aggressive course.

4). Gender: We observed that females with respiratory disease have similar status to males at enrollment and five year follow-up, but deteriorate markedly by ten year follow-up. Other investigators have noted that females have worse survival than males in the teen age years. Several hypotheses have been offered to explain these results, including poor compliance with therapy among females in the teen age years, and diminished strength among females in clearing secretions.[30] We also observed that the disproportionately large number of females presenting with respiratory disease also contributed to the worse overall outcomes among females in the cohort.

5). Staph aureus colonization: Patients colonized with staph at zero time were indistinguishable from the rest of the cohort at zero time and at five year follow-up, but had poor ten year outcomes. No other series has offered data on the prognostic effect of initial cultures for staph.

3. Pertinent negative findings: One possible consideration is that patients with the worst initial total Shwachman scores would deteriorate fastest. If that were the case, clinical features might have little further prognostic value. However, our data document clearly that the initial total score is of no value in predicting the clinical course. The clinical features discussed throughout this study provide much better indicators of prognosis than simple assessment of overall status by Shwachman score at zero time.

The age of patients in the cohort at zero time had no clear relation to subsequent outcomes either. As discussed in the Literature Review, no

previous study had adequately examined the prognostic significance of the age at zero time.

Finally, the secular period of enrollment had no prognostic value either. This finding is not surprising. The eligibility criteria for the study were designed in part to assure that the same basic therapeutic measures were available to all patients.

II. Implications for Clinical Management

From the descriptive and analytic findings of this study, we can delineate several profiles of patients with distinct clinical features at presentation and subsequent outcomes. This section will present four brief case histories of patients actually included in our study who typify these profiles. The cases will include one patient with steatorrhea, another with meconium ileus, and two with respiratory disease -- one with a relatively benign outcome and the other with an aggressive course. These cases do not encompass all of the features discussed in the study. For example, patients with isolated respiratory disease are not represented, as there were just eight such individuals in the study.

A. Steatorrhea

D.B. is a ten year old white male who was the product of a normal delivery to a family with no known history of cystic fibrosis. By one month of age his parents reported the stools to be foul-smelling, bulky, and greasy. After an episode of rectal prolapse at five months of age, he was sweat tested, and diagnosed as having CF. He had no clubbing at that time, and throat cultures revealed normal flora. Total Shwachman score at enrollment to the Yale clinic was 83 with a nutrition score of 18 and chest x-ray of 25. At five year follow-up, the patient's overall status improved

with a total score of 94. His chest film was still entirely normal (25) and with pancreatic enzyme supplementation, his nutrition score had improved to 23. By ten year follow-up the patient still had only minimal compromise in his daily activities. Total Shwachman score was 93 although the chest x-ray slipped to 22. An interesting addition to D.B.'s history is that he developed Coombs negative hemolytic anemia shortly after diagnosis, a rare complication of CF felt to be due to deficiency of Vitamin E.

Aside from the anemia, D.B.'s history is quite typical of patients presenting with steatorrhea. These children are often diagnosed at less than a year of age with normal chest x-rays. Their overall status improves with enzyme therapy and does not deteriorate until respiratory disease ensues. The recent change in chest x-ray score suggests that D.B. may begin to show progressive deterioration.

B. Meconium Ileus

T.G. is a nine year old white male born with meconium ileus relieved surgically but without resection. Sweat test in the neonatal period was positive. The patient had no respiratory symptoms at enrolment and throat cultures showed normal flora. Total score was 87 with a nutrition score of 18. By five years of follow-up, the patient was in excellent condition with an x-ray score of 24, a nutrition score of 23, and a total score of 97. Recently, at nine year follow-up, he had a chronic cough, mild clubbing, colonization with staph aureus, and chest film of 22. Total score had slipped to 93.

T.G. typifies the child with meconium ileus who survives the neonatal period and has a relatively mild course. Currently, these children do no worse than patients with CF with normal births. Like D.B., T.G. has just

recently shown respiratory involvement and can be expected to deteriorate slowly.

C. Respiratory Disease

L.N. is a ten year old female who was the product of a normal delivery. By six months of age, the mother reported a history of foul, bulky stools, and chronic cough to the pediatrician. When these symptoms persisted at nine months of age, the pediatrician ordered a sweat test which was positive. There was no history of pneumonia, no clubbing, and initial chest x-ray score was 25. Throat culture was positive for staphlococcus aureus. Total Shwachman was 91. By five years of follow-up, the patient had developed a productive cough, pseudomonas colonization, and moderate clubbing. Chest film score was 19 and total score was 84. At ten years the chest film dropped to 18 and total score to 83. The patient had been admitted several times for management of pseudomonas colonization and infection.

Steatorrhea led to the diagnosis in L.N.'s case, the respiratory disease being mild at enrollment. As the respiratory disease worsened, her overall status fell as well. However, it is noteworthy that by ten years of age she still had a "good" score. Hence, L.N. represents a child with combined gastrointestinal and respiratory disease at presentation, but with a relatively good outcome at ten years.

M.G. was born in 1969, the normal female product of a family with no history of CF. She had a chronic cough from birth and steatorrhea beginning around six months of age. By two years of age, these symptoms persisted and her local pediatrician performed a sweat test which was positive. At enrollment, she had no clubbing, negative throat cultures, and no pneumonia. Chest film was 24 and total score was 89. By five year follow-up, she had

recently shown respiratory involvement and can be expected to deteriorate slowly.

C. Respiratory Disease

L.N. is a ten year old female who was the product of a normal delivery. By six months of age, the mother reported a history of foul, bulky stools, and chronic cough to the pediatrician. When these symptoms persisted at nine months of age, the pediatrician ordered a sweat test which was positive. There was no history of pneumonia, no clubbing, and initial chest x-ray score was 25. Throat culture was positive for staphlococcus aureus. Total Shwachman was 91. By five years of follow-up, the patient had developed a productive cough, pseudomonas colonization, and moderate clubbing. Chest film score was 19 and total score was 84. At ten years the chest film dropped to 18 and total score to 83. The patient had been admitted several times for management of pseudomonas colonization and infection.

Steatorrhea led to the diagnosis in L.N.'s case, the respiratory disease being mild at enrollment. As the respiratory disease worsened, her overall status fell as well. However, it is noteworthy that by ten years of age she still had a "good" score. Hence, L.N. represents a child with combined gastrointestinal and respiratory disease at presentation, but with a relatively good outcome at ten years.

M.G. was born in 1969, the normal female product of a family with no history of CF. She had a chronic cough from birth and steatorrhea beginning around six months of age. By two years of age, these symptoms persisted and her local pediatrician performed a sweat test which was positive. At enrollment, she had no clubbing, negative throat cultures, and no pneumonia. Chest film was 24 and total score was 89. By five year follow-up, she had

pseudomonas colonization and a chest film of 20. Total score was still 89, however, as her nutritional status had improved from enrollment. By ten years her respiratory disease had worsened markedly, her chest x-ray being 15 and total score 20. She had recently been admitted for anti-pseudomonal therapy. She died at twelve year of age.

M.G.'s history reflects the aggressive course that the disease often takes in patients (especially females) with onset of respiratory symptoms early in infancy.

While these vignettes do not touch upon all of the issues discussed in this study, the histories do support the principal conclusions. First, it is important to note that except for M.G., these patients generally had good scores ten years after enrollment. This phenomenon is representative of the cohort as a whole after ten years. The challenge for clinicians is to identify those patients who will deteriorate fastest. Clearly, the initial total scores are of no help, as D.B. and T.G. had the lowest initial scores but the mildest subsequent clinical courses. The mode of presentation is more helpful: The first two cases reflect that overall status of patients without respiratory disease often improves with pancreatic enzyme supplementation and does not deteriorate substantially until the onset of respiratory disease. In contrast, the third and fourth cases reflect the finding that patients with respiratory disease at the onset deteriorate faster. This distinction in the clinical significance of respiratory and gastrointestinal involvement is the central theme emerging from histories of the patients in our study.

III. Implications for Clinical Research

The recognition of prognostically distinct groups of patients also has implications for clinical research. For example, a clinical trial of therapeutic interventions would be biased if one group of subjects were represented disproportionately by patients with particularly favorable or unfavorable prognoses. Hence, investigators should assure that experimental cohorts have even representation of patients from prognostically distinct groups. Furthermore, particular interventions may only be effective or appropriate in select subgroups of patients. Therefore, in studying the efficacy of such measures, investigators should stratify their subjects into these distinct subgroups.

IV. Directions for Future Research

This study raises several unanswered questions which could be explored by further clinical research. Four broad areas for future study will be outlined briefly in this section.

A. The Prognostic Effect of Features Not Adequately Evaluated in This Study

Because some of the subgroups were quite small, we were unable to evaluate four features with statistical persuasiveness. These included co-morbid disease; the distinction between isolated respiratory disease and combined respiratory and gastrointestinal disease; the outcomes of patients truly found to be asymptomatic at presentation; and the prognostic effect of alveolar disease at ten year follow-up. Study of a larger series might clarify the associations between these zero time findings and subsequent morbidity outcomes.

B. Diagnostic Stimulus vs. Symptoms Present at Presentation

It was apparent that the events leading to sweat test differed among patients who had very similar symptom status at zero time. It would be interesting to study the relationship between diagnostic stimulus and subsequent outcomes among patients with similar clinical presentations. Such an analysis would refine the present study by considering the variability in identification of patients with the likely diagnosis of cystic fibrosis.

C. Early vs. Late Onset of Respiratory Disease

We have shown that patients with onset of respiratory disease in the perinatal period have worse outcomes. It would be interesting to determine whether patients with onset after three months of age have less aggressive disease, or whether it is equally aggressive but simply arises later. In addition, it would be useful to evaluate the onset of respiratory disease at later points in the clinical course as we did in this study at three months of age.

D. Correlation With Pulmonary Function Tests

Currently most clinicians follow the progress of patients with cystic fibrosis with pulmonary function tests. However, as pointed out earlier, patients cannot perform PFT's until around six years of age. Hence, these tests cannot be used to characterize zero time status. Clinicians are left to describe the presentations in term of clinical features considered in this study. It would be useful, therefore, to correlate these clinical features at zero time with subsequent pulmonary function test parameters. The results would help clinicians integrate the clinical trends we have outlined into their conventional manner of following older patients. This proposal poses the larger question, already the focus of clinical research of whether PFT's in fact serve as accurate surrogates for overall clinical course.31

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APPENDICES

A. Data Extraction Form

B. Data Coding Form

C. Summary of Shwachman Clinical Scoring System

D. Summary of Brasfield X-Ray Scoring System

Date of Extraction: ___/___/___ Hospital Unit No. 98

Extractor: ________________ Appendix A Study No. ________________

DATA COLLECTION FORM -- CF STUDY

I. Demographic Information

Name ________________ Birth Date ___/___/___ Gender ___ Phone ______

Parents' Name ________________ Address ________________

Parents' Occupations: Father: ________________ Mother: ________________

Referring M.D. ________________ Town ________________ Phone ______

Number of Children in Family at Time of Enrollment ________________

Birth Order of Children ________________

II. Pre-Existing Conditions

A. Relative with CF: Yes ___ No ___ If yes, relationship ________________

Date Dx ___/___/___ Age at Dx ___ Age at Death ___

Principal Organ System at Dx ________________

B. Co-Morbidity: Yes ___ No ___ If yes, please describe below:

Disease	Yes	No	Description and Dates
Complications of Pregnancy			
Premature Birth			
RDS			
Neonatal Intubation			
Respiratory: Asthma			
Other Respiratory			
Cardiac			
Infectious Disease: Meningitis			
Date / / Organism			
Other ID			
Renal			
CNS: Mental Retardation			
Developmental Delay			
Other CNS			
Endocrine			

Clinical Itinerary of Principal Illness

A. **Earliest Signs and Symptoms** -- list dates and describe:

____

____

____

____

____

B. **Hospitalization for Principal Illness** -- list dates and diagnoses:

1. ____
2. ____
3. ____
4. ____

C. **Signal Events Raising Suspicion of CF** -- list dates, symptoms, signs, labs, and diagnostic imaging

____

____

____

____

____

D. **Iatrotropic Stimulus for Sweat Testing:** ______________________________

____

E. **Sweat Test:** Yes ___ No ___

Date ___/___/___ Location ____________________ Result ____________________

F. **CF Dx Dates:**

1. Initial Suspicion ___/___/___
2. Plan to Sweat Test ___/___/___
3. Sweat Test ___/___/___
4. Referral to Clinic ___/___/___
5. Enrollment ___/___/___

G. Hospitalizations for IV Antibiotic Therapy

	Date	Duration	Treatment/Drugs Administered
1.	___/___/___		
2.	___/___/___		
3.	___/___/___		
4.	___/___/___		
5.	___/___/___		

H. Other Hospitalizations

	Date	Duration	Indication	Treatment
1.	___/___/___			
2.	___/___/___			

I. Weight Gain

Time	Wt.	%	Time	Wt.	%	Subsequent Follow-Up Dates	Wt.	%
Birth			Diagnosis					
1 yr			Enrollment					
5 yrs			2 yr fellow					
10 yrs			5 yr fellow					

V. Appearance of Symptoms and Signs

Category	Yes	No	Date of App.	Date of Disapp.	Description
Respiratory					
Wheezing					
Clubbing					
Cyanosis					
Hemoptysis (>1 cup)					
Cor Pulmonale					
Atelectasis					
Pneumothorax					
Mucoid Pseudomonas Colonization					
Staph Colonization					
Haemophilus Colonization					
GI					
Meconium Ileus (MI)					
Complication of MI-list					
Meconium Plug Syndrome					
Wt. <5th %					
Steatorrhea					

Category	Yes	No	Date of App.	Date of Disapp.	Description
Hypoproteinemia/Edema					
Biliary Cirrhosis					
Rectal Prolapse					
Vitamin Deficiency					
Pancreatitis					

Other

Diabetes Mellitus					
Azoospermia					
Nasal Polyps					
Heat Prostration/Salt Depletion					
Other					

V. Follow-Up

Date of Death ___/___/___

Date of Loss to Follow-Up ___/___/___ Reason ________________________________

CODING FORM

Appendix B

ame ______________________

ate Coded ________________

(1) Unit Number

] [ ] [ ] [ ] [ ] [ ] [ ]
1 2 3 4 5 6 7

(2) Card Number

[ ]
8

(3) Date of Birth

[ ] [ ] Month [ ] [ ] Year
9 10 11 12

(4) ID Number

[ ] [ ] [ ]
13 14 15

(5) Gender

[ ] 16
1 = Male
2 = Female

(6) Race

[ ] 17
1 = Black
2 = White
3 = Hispanic

(7) Age At ZT

[ ] [ ] [ ] Months
18 19 20

(8) Date Of ZT

[ ] [ ] Month [ ] [ ] Year
21 22 23 24

(9) Date of Dx

[ ] [ ] Month [ ] [ ] Yea
25 26 27 28

PRE-ZT CO-MORBIDITY:

(10) # Sibs With CF At ZT

[ ]
29

(11) Prematurity

[ ] 30
1 = Yes
2 = No

(12) RDS

[ ] 31
1 = Yes
2 = No

(13) Neonatal Sepsis

[ ] 32
1 = Yes
2 = No

(14) Other Co-morbidity

[ ] 33
0 = None
1 = g-e
2 = Bilary Artesia
3 = Hypothyroid
4 = Meconium aspiration
5 = Meconium plug
6 = Hirshprungs
7 = Aliac disease

(15) Birth To Onset of Sx

[ ] [ ] [ ] # Months
34 35 36
enter 999 if uncertain;
888 if asx at ZT

(16) Onset Sx To ZT

[ ] [ ] [ ] Same as (15)
37 38 39

(17) Pre ZT Hosp. (Resp.)

[ ] 40
0 = 0
1 = 1
Etc.

(18) Pre-ZT Hosp. (GI)

[ ] 41
0 = 0
1 = 1
Etc.

) Pre-ZT Hosp. (Resp. & GI)

[ ] 42
0 = 0
1 = 1
Etc.

(20) Resp. Sx At ZT

[ ] 43
0 = None
1 = Recus. Pneumonia
2 = Recur. Bronchitis
3 = chronic Cough
4 = Wheezing
5 = Acute Pneumonitis
6 = Resp. Sx, n.b.s.
9 = Unknown, Uncertain

103

(21) Resp. Sx At ZT

[ ] 44
Same as (20)

) Resp. Sx At ZT

] 5
Same as (20)

(23) GI Sx At ZT

[ ] 46
0 = None
1 = Steatorrhea
2 = Rectal Prolapse × 1
3 = Recurrent Prolapse
4 = Abdominal Pain
5 = Poor Weight Gain
6 = Mecileus
7 = GI, WOS
8 = Constipation
9 = Unknown

(24) GI Sx At ZT

[ ] 47
Same as (46)

) GI Sx At ZT

Same as (46)

(26) Other Sx At ZT

[ ] 49
0 = None
1 = Hx Coombs - Anemia
2 = Hx Hyponatremic Dehydration
3 = Hx Hypoproteinemic Edema
4 = Biliary Cirrhosis
5 = Nasal Polyps
6 = Femoral Hernias
7 = Increased LFT's
8 = Glucose intolerance

(27) Other Sx At ZT

[ ] 50
Same as (26)

(28) Signal Event Leading to Dx

[ ] 52
01 = Hx, ASX
02 = Mec. Ileus, No Surgery
03 = Mec. Ileus With Surgery; No Resection
04 = Mec. Ileus With Resection
05 = Mec. Ileus With Peritonitis
06 = Steatorrhea
07 = Rectal Prolapse; Hx Steatorrhea
08 = Steatorrhea In View Of Resp. Hx
09 = Abdominal Pain
10 = Nucocole of Appendix
11 = FTT Inpatient
12 = FTT Outpatient
13 = Recurrent Bronchitis
14 = Recurrent Pneumonia
15 = Acute Resp. Disease;Positive GI
16 = No Acute Event; Pos. GI & Resp. Hx
17 = Cholestatic Jaundice
18 = Hyponatremic Dehydration
19 = Hypoproteinemic Edema
20 = Coombs - Anemia
21 = Fam. Hx, With Sx
22 = Recurrent cough
23 = Recurrent wheeze

9) Diagnostic Setting

[ ] 53
1 = Ambulatory
2 = Hospital

(30) Clubbing At ZT

[ ] 54
0 = Absent
1 = Mild
2 = Moderate
3 = Severe

(31) Cultured At ZT?

[ ] 55
1 = Yes
2 = No

2) Pseudomonas At ZT

] 0 = Not Cultured
6 1 = Yes
2 = No

(33) Staph at ZT

[ ] 0 = Not Cultured
57 1 = Yes
2 = No

(34) Hemophilus At ZT

[ ] 0 = Not Cultured
58 1 = Yes
2 = No

5) Weight At Zt

[ ] [ ] #Kg
59 60

(36) Height At Zt

[ ] [ ] [ ] #cm
61 62 63

(37) Wt For Age At ZT

[ ]
64

1 = 0-5 %
2 = >5-10%
3 = >10-25%
4 = >25-50%
5 = >50-75%
6 = >75-90%
7 = >90%
9 = Unknown

8) Ht For Age At ZT

[ ] Same as (37)
65

(39) Wt For Ht At ZT

[ ] Same as (37)
66

(40) Pseudomonas Post ZT

[ ] [ ] Years Post ZT Until
67 68 + Culture
(Enter 00 if + At ZT; 99 If Never +)
88 if not cultured

(41) Staph Post ZT

] [ ] Same as (40)
9 70

(42) Hemophilus Post ZT

[ ] [ ] Same As (40)
71 72

(43) I.V. Cleanouts

[ ] Total #
73

[ ] [ ] Years AFter ZT
74 75 of First Admit
(99 If None)

44) G.I. Hosps. Post ZT

otal # [ ] [ ] Years After
77 78 ZT of 1st
Admit
(99 if none)

(45) Unit Number

[ ] [ ] [ ] [ ] [ ] [ ] [ ]
1 2 3 4 5 6 7

(46) Card #

[2]
8

47) Co-morbidity Post ZT

[ ] 1 = Yes
9

(48) Type Of Co-morbidity

[ ] 0 = None
10 1 = Arrhythmia
2 = Cholangitis

(49) Year Of Death

[ ] [ ] 00 = Alive
11 12

50) Status At 2 Years

[ ] 1 = Dead
13 2 = Alive
3 = LTFU

(51) Status At 5 Years

[ ] 1 = Dead
14 2 = Alive

(52) Status At 10 Years

[ ] 1 = Dead
15 2 = Alive
3 = LTFU
4 = Followed <10 Years

(3) Year Of Last FU

[ ] [ ]
16 17

(54) Status At Last FU

[ ] 1 = Dead
18

(55) Interval Between ZT & Death

[ ] [ ] [ ] # Months
19 20 21
Enter 888 If Alive
Enter 999 If Uncertain

(56) Interval Between Onset Sx And Death

[ ] [ ] [ ] Same As (55)
22 23 24

(57) Interval Between Dx And Death

[ ] [ ] [ ] Same As (55)
25 26 27

	ZT	2 Yrs	5 Yrs	10 Yrs	Recent
(8) Total Shwachman	[ ] [ ] [ ] 28 29 30	[ ] [ ] [ ] 31 32 33	[ ] [ ] [ ] 34 35 36	[ ] [ ] [ ] 37 38 39	[ ] [ ] [ ] 40 41 42
(9) Activity	[ ] [ ] 43 44	[ ] [ ] 45 46	[ ] [ ] 47 48	[ ] [ ] 49 50	[ ] [ ] 51 52
0) Physical Exam	[ ] [ ] 53 54	[ ] [ ] 55 56	[ ] [ ] 57 58	[ ] [ ] 59 60	[ ] [ ] 61 62
1) Nutrition	[ ] [ ] 63 64	[ ] [ ] 65 66	[ ] [ ] 67 68	[ ] [ ] 69 70	[ ] [ ] 71 72

(62) Unit #

[ ] [ ] [ ] [ ] [ ] [ ] [ ]
1 2 3 4 5 6 7

(63) Card #

[3]
8

4) X-Ray Total	[ ] [ ] 9 10	[ ] [ ] 11 12	[ ] [ ] 13 14	[ ] [ ] 15 16	[ ] [ ] 17 18
5) Air Trapping	[ ] 19	[ ] 20	[ ] 21	[ ] 22	[ ] 23
6) Bronchial Cuffing	[ ] 24	[ ] 25	[ ] 26	[ ] 27	[ ] 28
7) Small Lesions	[ ] 29	[ ] 30	[ ] 31	[ ] 32	[ ] 33
8) Large Lesions	[ ] 34	[ ] 35	[ ] 36	[ ] 37	[ ] 38
9) Overall Severity	[ ] 39	[ ] 40	[ ] 41	[ ] 42	[ ] 43

(Enter 0 If Patient Has Not Been Followed For the Length of Time Indicated. Round .5 Values To Lowest Whole Number.)

(70) Birth To Onset Of Resp Sx

[ ]
44

1 = 0-1 Month
2 = 1-3 Months
3 = 3-6 Months
4 = 6-12 Months
5 = 1-3 Years
6 = 3-5 Years
7 = 5-10 Years
8 = Greater Than 10 Years
9 = Unknown
0 = No Sx Before ZT

(71) Birth To Onset Of G.I. Sx

[ ] Same As In (44)
45

(72) Birth To Onset Of Other Sx

[ ] Same As In (44)
46

(73) Cause Of Death

[ ]
47

1 = Resp Decomp
2 = G.I. Decomp
3 = Accident
4 = Metabolic Imbalance
9 = Unknown

APPENDIX C

Grading*	Points	General Activity	Physical Exam	Nutrition	X-Ray Findings
Excellent (86-100)	25	Full normal activity	No abnormalities	Weight and height above 25th %ile Good muscle mass Stools almost normal	Clear lung fields
Good (71-85)	20	Tires at end of day Good school attendance	Rare cough No clubbing Clear lungs	Wt and Ht at 15th to 25th %ile Bulky stools Fair muscle mass	Slight broncho vascular markings and emphysema
Mild (56-70)	15	Exertional fatigue Rests during day Fair attendance	Mild clubbing rare rales Occas cough	Wt and Ht above 3d %ile Poorly formed stools abdom distens'n	Increased markings Patchy atelec. Mild emphys.
Moderate (41-55)	10	Rests after short walk Home teacher	Frequent cough Retractions 2-3+ clubbing Rales	Wt and Ht below 3d %ile Offensive stool Abdom distended	Widespread atelect Moderate emphysema
Severe (40 or below)	5	Orthopneic Confined to bed or chair	Severe cough Tachypnea Tachycardia 3-4+ clubbing	Malnourished Foul, frequent stools Protuberant abdomen	Lobar atelectasis Bronchiectasis

*Note that our clinical categories differ from those described by Shwachman. e.g. excellent = 90-100 in our study. We chose to categorize according to the clinic director's assessment of which numerical intervals corresponded to distinct managment strategies.

APPENDIX D

Summary of Brasfield X-Ray Scoring System

Abnormality	Comments	Scoring (demerit points)
Air trapping	Generalized over-distension manifest as sternal bowing, depressed diaphragms, or thoracic kyphosis	0 = absent 1 2 increasing 3 severity 4
Linear markings	Parrallel, branching or "end-on" circular densities with thickening of bronchial wall	0 = absent 1 2 increasing 3 severity 4
Nodular-cystic lesions	Multiple, discrete small rounded densities, 0.5cm in diameter or larger	0 = absent 1 2 increasing 3 severity 4
Large lesions	Segmental or lobar atelectasis or consolidation; includes acute pneumonia	0 = absent 3 = segmental or lobar atelectasis 5 = multiple atelectasis
General severity	Impression of overall severity of x-ray changes	0 = absent 1 2 increasing 3 severity 4 5 = complications (e.g. pneumothorax, cardiac enlargement)

Total score = 25 minus total demerit points

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